METHOD AND COMPOSITIONS FOR IDENTIFYING ANTI-HIV THERAPEUTIC COMPOUNDS

This non-provisional application claims the benefit of Provisional Application No. 60/375,622, filed April 26, 2002, Provisional Application No. 60/375,779 filed April

5   26, 2002, Provisional Application No. 60/375,834 filed April 26, 2002 and Provisional Application No. 60/375,665 filed April 26, 2002, which are incorporated herein by reference. Additionally, copending applications Attorney Docket Nos. 257.P2C and 260.PC filed concurrently with this application are also incorporated herein by reference in their entirety.

Field of the Invention

10   The invention relates generally to methods and compositions for identifying compounds having therapeutic activity against human immunodeficiency virus (HIV).

Background of the Invention

Anti-HIV compounds are well established and have achieved significant therapeutic benefit. However, existing therapeutics remain less than optimal. Conspiring to reduce

15   patient compliance and therapeutic efficacy are toxicity, resistant HIV, poor bioavailability, low potency, and frequent and inconvenient dosing schedules, among other failings. The need to administer very large tablets and requirements for frequent dosing characterize a number of important anti-HIV therapeutics, most particularly the HIV protease inhibitors. While significant advances have been made in preparing improved nucleotide analogue anti-

20   HIV therapeutics (see WO 02/08241, EP 820,461 and WO 95/07920, all of which are hereby incorporated by reference), other anti-HIV therapeutic drug classes remain encumbered with severe deficiencies.

Summary of the Invention

The present invention provides methods and compositions for identifying therapeutic

25   anti-HIV compounds having improved pharmacological and therapeutic properties. In particular, this invention provides for novel candidate therapeutic anti-HIV compounds and methods for screening them to identify compounds having such beneficial properties.

In accordance with this invention, a method is provided that comprises

(a) identifying a non-nucleotide prototype compound;

30   (b) substituting the prototype compound with an esterified carboxyl or esterified phosphonate-containing group to produce a candidate compound; and

(c) determining the anti-HIV activity of the candidate compound.

In another embodiment, a method is provided that comprises

    (a) selecting a non-nucleotide candidate compound containing at least one esterified

5   carboxyl or esterified phosphonate-containing group and

    (b) determining the intracellular persistence of the candidate compound or a esterolytic

        metabolite of the esterified carboxyl or phosphonate-containing group thereof.

In a further embodiment, determining the anti-HIV activity of the candidate compound

10   comprises determining the anti-HIV activity of a carboxylic acid or phosphonic acid-

containing metabolite of the candidate compound, which carboxyl acid or phosphonic acid-

containing metabolite is produced by esterolytic metabolic cleavage of the esterified carboxyl

or phosphonate-containing group. In another embodiment determining anti-HIV activity

comprises determining the the tissue selectivity and/or the intracellular residence time of at

15   least one of said intracellular carboxylic acid or phosphonic acid-containing metabolites.

In another embodiment of this invention, a library of anti-HIV candidate compounds is

provided that comprises at least one non-nucleotide prototype compound substituted by an

esterified carboxyl or phosphonate group. Such libraries facilitate large-scale screening of

20   candidate compounds.

This invention is an improvement in the conventional methods for identifying

therapeutic anti-HIV compounds. Thus, in a method for identifying an anti-HIV therapeutic

compound, the improvement comprises substituting a prototype compound with an esterified

25   carboxyl or phosphonate and assaying the resulting candidate compound for its anti-HIV

activity.

Adding the esterified carboxyl or phosphonate group to the prototype molecule

produces significant advantages in the pharmacologic properties of the prototype. Without

30   being held to any particular method of operation of the invention, it is believed that the ester(s)

mask the charge of the carboxyl or phosphonate and permit the candidate to enter HIV

infected cells, in particular peripheral blood mononuclear cells (PBMCs). Once the candidate

has entered the cells it is processed by biological mechanisms (most notably, it is believed, by a

newly discovered PBMC enzyme which we designate GS-7340 Ester Hydrolase) to produce at

35   least one metabolite containing a free carboxylic acid and/or phosphonic acid. This metabolite

is antivirally active against HIV. These charged metabolic depot forms are exceptionally persistent in the cells, thereby permitting substantial reductions in the frequency of dosing compared to the parental prototype, among other advantages. In addition, the esterified carboxyl or phosphonate substituent may direct the selective distribution of the prototype to
5   tissues (most particularly lymphoid tissues such as PBMCs) which are noted sites of HIV infection, thereby potentially reducing systemic dose and toxicity.

In further embodiments, assaying for anti-HIV activity optionally comprises screening the candidate compounds for their susceptibility to esterolytic cleavage by isolated GS-7340
10   Ester Hydrolase. The isolated Hydrolase is a further embodiment of this invention.

Since GS-7340 Ester Hydrolase may interact with other compounds than the anti-HIV candidates, it will be of pharmacologic utility to determine if the enzyme is cleaving such other compounds. Thus, another embodiment of this invention is a method comprising obtaining a
15   substantially pure organic molecule, optionally contacting the organic molecule with another molecule to produce a composition, contacting GS-7340 Ester Hydrolase with said organic molecule or composition, and optionally determining whether the organic molecule has been cleaved by the Hydrolase.

In another embodiment, a method is provided comprising contacting GS-7340 Ester
20   Hydrolase with an organic compound in a cell-free environment.

In a further embodiment, a method is provided comprising contacting GS-7340 Ester Hydrolase with an organic compound in an *in vitro* or cell culture environment.

In another embodiment, a composition is provided comprising a substantially pure organic compound and isolated GS-7340 Ester Hydrolase.
25   In another embodiment, a composition is provided comprising an organic compound and GS-7340 Ester Hydrolase in an *in vitro* or cell culture environment.

These and other embodiments of this invention are more fully described in the following disclosure.

Detailed Description of the Invention

The following disclosure contains detailed embodiments of the practice of the invention. These are provided to more fully describe the invention, but the invention is not limited to these embodiments.

5

"Anti-HIV activity" of candidates is determined by any method for assaying the HIV inhibitory activity of a substance. Many such methods are well known, and range from *in vitro* enzyme assays (e.g., HIV reverse transcriptase or integrase assays) to animal studies (e.g., SIV in chimps) and human clinical trials. Included with this term are any assays bearing on the

10   therapeutic anti-HIV efficacy of a substance, e.g., HIV resistance determinations, biodistribution, and intracellular persistence.

"Candidate compound" is an organic compound containing an esterified carboxylate or phosphonate. Optionally, candidate compounds excluded compounds heretofore known to

15   have anti-HIV activity. With respect to the United States, the candidate compounds herein exclude compounds that are anticipated under 35 USC §102 or obvious under 35 USC §103 over the prior art. In other jurisdictions using the novelty and inventive step criteria, the candidate compounds exclude compounds not novel or which lack inventive step over the prior art. However, libraries containing candidate compounds optionally comprise known

20   compounds. These may be, for example, reference compounds having known anti-HIV activity.

"Non-nucleotide" means any compound that has all of the following characteristics: It does not already contain an esterified carboxyl or phosphonate, it is not a phosphonate or

25   phosphate-containing compound disclosed in WO 02/08241, EP 820,461 or WO 95/07920 and it does not already contain a phosphonate group. GS-7340 is an example of a nucleotide anti-HIV compound. Many other examples of such compounds are known. These compounds are excluded from the scope of prototype compounds and are not employed in the candidate compound screening method or candidate compound ompositions of this invention.

30   For the most part, the nucleotide analogues comprise the substructure $-OC(H)_2P(O)=$ coupled (usually at the 9 position of purine bases or the 1 position of pyrimidine bases) via a sugar or cyclic or acyclic sugar analogue (aglycon) to a nucleotide base or an analogue thereof. The base analogues typically are substituted, usually at extracyclic N atoms, or are the aza or deaza

analogues of the naturally occuring base scaffolds. They are fully set forth in the above described art and are well known in the field. See for example U.S. Patent 5,641,763 and related patents and publications by Antonin Holy.

5   Optionally excluded from the scope of the libraries of this invention are any phosphonates disclosed by WO99/33815, WO99/33792, WO99/33793, WO00/76961 and their related, progeny and parental filings, all of which are hereby incorporated by reference. However, unless expressly excluded by the claims herein, such compounds shall be considered candidate compounds. Further, the act of making and screening the phosphonates of such

10   filings to determine their intracellular persistence (whether by preclinical assays such as that using GS-7340 Ester Hydrolase, or by clinical studies) falls within the scope hereof, as does obtaining regulatory approval to market one of them and selling the selected phosphonate.

"Non-nucleoside" means any compound that is not a nucleotide base linked to a sugar

15   or aglycon (cyclic or acyclic) and terminating at the 5' position (or the analogous position in nucleosides containing sugar analogues) by hydroxyl or a group which is metabolized *in vivo* to hydroxyl. The nucleosides are distinguishable from the nucleotides in not containing a phosphate or, in the case of relevant nucleotide analogues, a phosphonate.

20   "Phosphonate-containing group" is a group comprising a phosphorus atom singly bonded to carbon, double bonded to oxygen and singly bonded to two other groups through oxygen, sulfur, or nitrogen. In general, the carbon bond is to a carbon atom of the prototype or a linking group to the prototype and the single bonds to oxygen, nitrogen or sulfur are bonds to oxy or thioesters or are amino acid amidates in which the terminal carboxyl group(s)
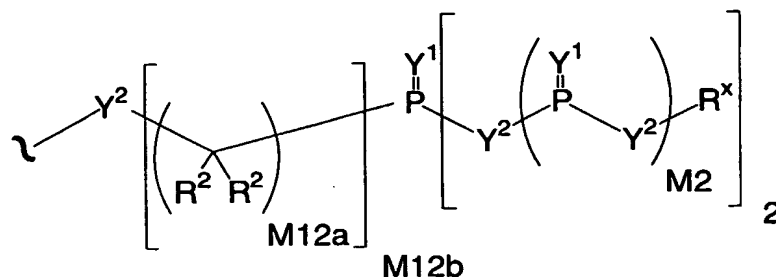
25   are esterified.

"Carboxyl-containing groups" are any group having a free carboxyl serving as the site for esterification. An "organic acid" is any compound containing carboxyl and at least one additional carbon atom.

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The "esterified carboxyl or esterified phosphonate group" is any group capable of intracellular processing to yield a free carboxyl and/or free phosphonic acid. The structure of these groups is not important other than that the free acid be produced intracellularly. Preferably, systemic or digestive esterolysis is minimized in preference to intracellular

hydrolysis. This permits maximum migration of the candidate into target cells and maximum intracellular retention of the acid metabolites.
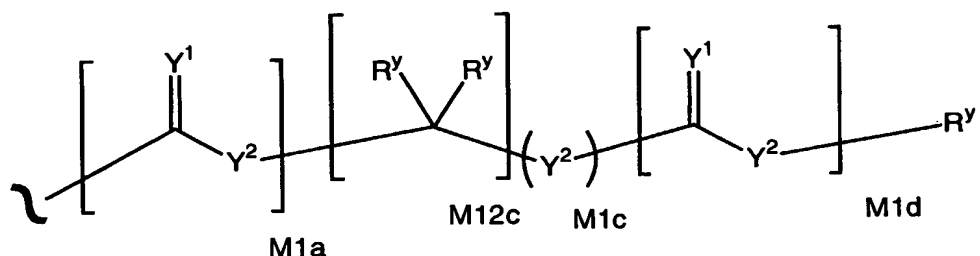
Suitable exemplary esterified carboxyl or phosphonate groups are described herein. Others are identified by screening for esterolysis *in vivo*, in PBMCs or using GS-7340 Ester Hydrolase. These groups have the structure A^3, wherein A^3 is a group of the formula

$$\text{Y}^2 \left[\left(\text{C} \overset{R^2}{\underset{R^2}{\big|}} \right)_{M12a} \right]_{M12b} - \overset{Y^1}{\underset{\parallel}{P}} \left[\text{Y}^2 \left(\overset{Y^1}{\underset{\parallel}{P}} \right) \text{Y}^2 \right] R^x \Big]_{M2} \Big]_2$$

in which:

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, -$S(O)_{M2}$-, or -$S(O)_{M2}$-$S(O)_{M2}$-;

R^x is independently H, W^3, a protecting group, or a group of the formula:

$$\left[\overset{Y^1}{\underset{\parallel}{C}} \text{Y}^2 \right]_{M1a} \left[\overset{R^y}{\underset{}{C}} \overset{R^y}{} (\text{Y}^2)_{M12c} \right]_{M1c} \left[\overset{Y^1}{\underset{\parallel}{C}} \text{Y}^2 \right]_{M1d} R^y \quad ;$$

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or -NO_2;

R^{3b} is Y^1;

R^{3c} is -R^x, -$N(R^x)(R^x)$, -SR^x, -$S(O)R^x$, -$S(O)_2R^x$, -$S(O)(OR^x)$, -$S(O)_2(OR^x)$, -$OC(Y^1)R^x$, -$OC(Y^1)OR^x$, -$OC(Y^1)(N(R^x)(R^x))$, -$SC(Y^1)R^x$, -$SC(Y^1)OR^x$, -$SC(Y^1)(N(R^x)(R^x))$, -$N(R^x)C(Y^1)R^x$, -$N(R^x)C(Y^1)OR^x$, or -$N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

The esterified group is attached to the prototype through a bond or via intermediary linking groups such as the A^1 subgroup $-[Y^2-(C(R^2)_2)_{m12a}]_{m12b}Y^2W^6-$ defined below.

Candidates optionally are substituted with a single substituent which contains both an esterified carboxyl and an esterified phosphonate. In addition, or as an alternative, the candidate contains separate substituents bearing esterified carboxyl and/or phosphonate groups. An example of a combined group would a phosphonate in which a free valence of the phosphorus atom is bonded to the hydroxy of an hydroxyorganic acid or to the amino group of an amino acid wherein the carboxyl groups of the organic acid or amino acid are esterifed.

"Esterified" means that the phosphonate or carboxyl is bonded to a carbon atom-containing group through oxygen or sulfur, as in $-P(O)(OR)-$ or $-COOR$ for example, where R is a carbon containing group such as alkyl or aryl.

"Protecting group" is a group covalently bonded to a labile site on the candidate

compound, which site is expected to be labile under the conditions to be encountered by the candidate, for example during synthetic procedures, during exposure to ambient conditions, and the conditions found in *in vivo* environments. The protecting group serves to prevent degradation or otherwise undesired conversions at the labile site. Extensive disclosure of

5   various exemplary protecting groups is found *infra*.

"Intracellular depot metabolite" is an esterolytic metabolite of the esterified carboxyl or phosphonate whereby a charged carboxyl or phosphonic acid is revealed. An example is Metabolite X, further described in the examples.

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"Tissue selectivity" of candidate compounds is determined by procedures set forth in WO02/08241. The object of this determination is to find whether or not the candidate (and by extension its depot forms) are enriched in one tissue or another. It is expected that compounds containing the carboxyl or phosphonate groups as described herein will be

15   preferentially enriched in lymphoid tissue such as PBMCs.

"Intracellular residence time," "intracellular persistence," "intracellular half life" and the like refers to a measure of the time that a candidate molecule or its anti-HIV active metabolite is found within a given cell after introduction of the esterified candidate into the

20   cell. Any technique is suitable that demonstrates how long a candidate or its anti-HIV active metabolite(s) remain in a cell. Further description of suitable assay procedures are set forth *infra*. Ideally, the method for measuring residence time will measure the retention time of the metabolite at a concentration adequate to inhibit HIV.

25   A "prototype compound" is any organic compound. In general, in the method of this invention one will select prototype compounds having known structures and synthesis routes in order to reduce the synthetic burden and development costs. Typically, the prototype compound will be one that has, or at least is suspected, to have anti-HIV activity. However, since the prototype compound is serving only as a starting point for preparing candidate

30   compounds to be screened, it is not essential that it have, or be known or suspected to have, preexisting anti-HIV activity. The prototype compound need not be published or known generally to the public. In fact, the method of this invention is advantageously practiced in on-going proprietary research programs where anti-HIV compounds are continually identified and optimized. It also should be understood that identification or selection of the prototype

compound need not be temporally related to that of the candidate compound. This means that the prototype might be identified after one or more related candidate compounds are made, or the prototype might be an early version of a compound class that has advanced further into development before the candidate based on the early prototype is actually synthesized. The

5   prototype compound also may be entirely conceptual or may be in various phases of development. No actual prototype need to have been made, nor tested for activity or any other properties. This is often the case with candidates that are the product of truncating an existing compound and then inserting a linker group in place of all or a part of the omitted portion. In addition, it is not necessary that the prototype compound be conceived

10   independently of the esterified substituent, i.e., it is not necessary to have the prototype in mind before designing the esterified substitution. The conception of the candidate compound optionally is a single act. Of course, the candidate compound may be based on a prototype which is in fact a previously made candidate compound and the subsequent candidate is multiply substituted with the carboxyl or phosphonate ester. Also, it will be understood that a

15   candidate or group of candidates compounds optionally are based on an original prototype even though intervening candidates or libraries of candidates have been made.

The prototypes generally serve as the starting point for designing and identifying candidate compounds. Generally a prototype will not contain a phosphonate or carboxyl

20   group, but it may do so if the phosphonate or carboxyl are not esterified (since candidates contain esterified phosphonate or carboxyl groups). It is most efficient to start with prototypes already known to have anti-HIV activity (preferably compounds active against anti-HIV protease, HIV integrase or HIV polymerase), but it is not essential to do so. For example, a prototype optionally is a subsegment or fragment of a compound known to possess

25   anti-HIV activity, even though the fragment need not be active against HIV in its own right. In this instance, the phosphonate or carboxyl group restores anti-HIV activity to the candidate.

"Linker" or "link" is a bond or an assembly of atoms binding the prototype to the the

30   esterified phosphonate or carboxyl-containing group. The nature of the linker is not critical. The linker need not be involved in the interactions of the esterified carboxyl or phosphonate group with GS-7340 Ester Hydrolase or other processing enzymes, nor need it be involved in the therapeutic interaction of the prototype with its target protein. This is not to say that these functions could not be enhanced or influenced by the linker, but it is not necessary that the

linker perform or contribute to such functions. Thus, it is a straight-forward matter of elemental organic chemistry to devise suitable linkergroups and methods for joining the esterified groups.

5   Some general principles are useful in selecting suitable linkergroups, despite their lack of criticality. First, they will not be so bulky as to interfere with the interaction of the remainder of the prototype with its target protein, e.g., HIV protease inhibitor, nor will they bear reactive or unstable groups once the linkage has been accomplished. Such chemically reactive groups will be well known to the artisan, and the parameters of bulky linkers can be

10   evaluated by molecular modeling. Resources are available to model proteins involved in a number of diseases and disorders of lymphoid tissues, in particular HIV protease. In general, the linker will be relatively small, on the order of about 16-500 MW, typically about 16-250, ordinarily about 16-200, although as noted the linker can be as small as a bond. It generally will be substantially linear, containing less than about 40% of the total MW of the linkeratoms

15   being found in branching groups, typically less than 30% and ordinarily less than about 20%.

The backbone of such linkergroups ideally will not contain any atom that is known to be labile to cleavage by biological processes or otherwise subject to hydrolysis in biological fluids. Typical suspect groups would be esters or amides in the backbone of the linker. The

20   object is for the carboxyl or phosphonate to survive intracellular processing, with only the ester(s) being hydrolyzed, and the presence of labile groups in the backbone would jeopardize this function. However, if enzymatic access to labile atoms or groups is sterically hindered, e.g., by a cycloalkyl group or branched alkyl group, then labile sites optionally may be used in the linker. Labile groups also optionally are can be found in locations other than backbone

25   positions, e.g. on branching groups or cyclic substituents, where their potential cleavage would not result in the loss of the free acid functionality. Backbone alkyls, alkyl ethers (S or O), or alkyl containing N in any oxidation state are usually satisfactory. Generally the linker backbone is linear rather than branched or cyclic (although it may be desired to use branching or cyclic backbones when multiple esterified groups are substituted onto the prototype). The

30   linker generally is chosen to permit substantial rotational freedom to the esterified group, and for this reason backbone double or triple bonds are not favored unless it is expected that they would be metabolized to less rotationally confined structures *in vivo* (e.g., oxidized to hydroxyl substituents). If it is desired to avoid interactions with the target protein then the

linker optimally will have neither highly charged nor strongly hydrophobic character, although as noted such properties can have advantages in enhancing anti-HIV activity.

5   The typical linker to phosphonate will comprise at least the group –OCH$_2$- (wherein the carbon is linked to the phosphorous atom), but many others will be apparent to the artisan or are described elsewhere herein.

Synthetic ease optionally will play a role in selection of the linker. For this reason, many linkers will contain a backbone or chain heteroatom such as 1 to 3 S, N or O. However,
10   occasionally the prototype compound will contain a convenient site for insertion of the linker, e.g., a pendant hydroxyl, thus enabling a small linkergroup because the phosphorous atom can be linked directly, or virtually directly, to the prototype. Synthetic routes also can be devised readily that permit direct linkage of the phosphorous atom to the prototype, in which case the linker is merely a bond.

15

The linker optionally is grafted onto the prototype, or the prototype compound is optionally is modified to remove group(s) which then are replaced with linker(s). This may facilitate the synthesis of the candidate compound or, in some instances, may fortuitously improve the properties of the candidate. This may or may not be more efficient that simply
20   grafting A^3 onto the prototype.

Typically, the starting point in devising a facile synthetic route for a candidate compound is to analyze the synthons employed in known methods for preparing the remainder of the prototype compound, concentrating on synthons which could contribute at least a part
25   of the esterified group. Such synthons optionally are modified to contain the esterified group or a portion thereof (e.g., the acid, which is then esterified in a later step). They are then introduced into the remainder of the candidate in substantially the same fashion as the prototype or antecedent compound. Alternatively, a reactive group is introduced into the synthon before it is assembled into the precursor, and it is this group that is reacted with an
30   intermediate for the carboxyl or phosphonate group. If necessary, suitable protecting groups are employed to facilitate the synthesis.

The site for insertion of the esterified carboxyl or phosphonate group on the prototype will vary widely. The esterified group preferably is substituted at any location on the

prototype that does not bind substantially with the target protein or affect the functioning of a group that does interact with the target protein. These sites are identified by molecular modeling, by consulting systematic SAR studies or by preparing pilot candidate compounds. However, it is also within the scope of this invention to insert the esterified groups at a site

5   which is involved in binding the prototype to the target protein. Such sites optionally are used if (a) the linker reasonably replicates the function of the group on the prototype that it is displacing, e.g., it possesses a side chain containing the group, (b) if the loss in binding affinity is not critical to the functioning of the prototype or (c) if other substitutents are introduced into the prototype that compensate for any loss in activity caused by the insertion of the linker.

10

The linker generally will contain at least two free valences (1 for the prototype and 1-3 for the esterified groups). Multivalent linkergroups can be employed to form a cyclic structure, being joined at 2 or more sites on the prototype and forming a bridge, the bridge in turn being subsituted with one or more esterified carboxyl or phosphonate groups or including

15   at least one atom encompassed within such groups. In addition, the linker does not need to be bound to the esterified group and/or the remainder of the prototype by a covalent bond, nor need it consist solely of covalently bonded atoms. Any bond meeting the basic criteria herein will be satisfactory, as for example linkage by chelation or other stable non-covalent attachment systems are included within the scope of the term "bond" as used herein.

20

Linkers also include polymers, e.g., those containing repeating units of alkyloxy (e.g. polyethylenoxy, PEG, polymethyleneoxy) and/or alkylamino (e.g. polyethyleneamino, Jeffamine™). Other linker groups include diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

25

Suitable linker groups optionally are prescreened by testing model candidates in the same fashion set forth herein for disclosed candidate compounds, e.g., screening using the Ester Hydrolase described herein, or by studying the effect of a model linker-containing candidate compound in PBMCs.

30

Typical linkers have the A^1 substructure $-[Y^2-(C(R^2)_2)_{m12a}]_{m12b}Y^2W^6-$ wherein Y^2, R^2, m12a and m12b are defined elsewhere herein, W^6 is W^3 having from 1 to 3 free valences and the prototype is bound to the Y^2 with free valence. However, many other structures would be

apparent to the ordinary artisan and can be prepared by conventional means using the guidance herein.

Defined Chemical Terms

"Alkyl" is C_1-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, -CH3), ethyl (Et, -CH2CH3), 1-propyl (n-Pr, n-propyl, -CH2CH2CH3), 2-propyl (i-Pr, i-propyl, -CH(CH3)2), 1-butyl (n-Bu, n-butyl, -CH2CH2CH2CH3), 2-methyl-1-propyl (i-Bu, i-butyl, -CH2CH(CH3)2), 2-butyl (s-Bu, s-butyl, -CH(CH3)CH2CH3), 2-methyl-2-propyl (t-Bu, t-butyl, -C(CH3)3), 1-pentyl (n-pentyl, -CH2CH2CH2CH2CH3), 2-pentyl (-CH(CH3)CH2CH2CH3), 3-pentyl (-CH(CH2CH3)2), 2-methyl-2-butyl (-C(CH3)2CH2CH3), 3-methyl-2-butyl (-CH(CH3)CH(CH3)2), 3-methyl-1-butyl (-CH2CH2CH(CH3)2), 2-methyl-1-butyl (-CH2CH(CH3)CH2CH3), 1-hexyl (-CH2CH2CH2CH2CH2CH3), 2-hexyl (-CH(CH3)CH2CH2CH2CH3), 3-hexyl (-CH(CH2CH3)(CH2CH2CH3)), 2-methyl-2-pentyl (-C(CH3)2CH2CH2CH3), 3-methyl-2-pentyl (-CH(CH3)CH(CH3)CH2CH3), 4-methyl-2-pentyl (-CH(CH3)CH2CH(CH3)2), 3-methyl-3-pentyl (-C(CH3)(CH2CH3)2), 2-methyl-3-pentyl (-CH(CH2CH3)CH(CH3)2), 2,3-dimethyl-2-butyl (-C(CH3)2CH(CH3)2), 3,3-dimethyl-2-butyl (-CH(CH3)C(CH3)3.

"Alkenyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp^2 double bond. Examples include, but are not limited to: ethylene or vinyl (-CH=CH2), allyl (-CH2CH=CH2), cyclopentenyl (-C5H7), and 5-hexenyl (-CH2CH2CH2CH2CH=CH2)

"Alkynyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, sp triple bond. Examples include, but are not limited to: acetylenic (-C≡CH) and propargyl (-CH2C≡CH),

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to: methylene (-CH2-) 1,2-ethyl (-CH2CH2-), 1,3-propyl (-CH2CH2CH2-), 1,4-butyl (-CH2CH2CH2CH2-), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to: 1,2-ethylene

5   (-CH=CH-).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. Typical alkynylene radicals include, but are not limited to: acetylene ($-C{\equiv}C-$),

10   propargyl ($-CH_2C{\equiv}C-$), and 4-pentynyl ($-CH_2CH_2CH_2C{\equiv}CH-$).

"Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from benzene,

15   substituted benzene, naphthalene, anthracene, biphenyl, and the like.

"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-

20   phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group comprises 6 to 20 carbon atoms, e.g. the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 5 to 14 carbon atoms.

25   "Substituted alkyl", "substituted aryl", and "substituted arylalkyl" mean alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a substituent. Typical substituents include, but are not limited to, -X, -R, -O⁻, -OR, -SR, -S⁻, $-NR_2$, $-NR_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, NC(=O)R, -C(=O)R, -C(=O)NRR $-S(=O)_2O^-$, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, -

30     $S(=O)_2NR$, -S(=O)R, $-OP(=O)O_2RR$, $-P(=O)O_2RR$ $-P(=O)(O^-)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)X, -C(S)R, -C(O)OR, -C(O)O⁻, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(NR)NRR, where each X is independently a halogen: F, Cl, Br, or I; and each R is

independently -H, alkyl, aryl, heterocycle, protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

"Heterocycle" as used herein includes by way of example and not limitation these
5   heterocycles described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566.
10

Examples of heterocycles include by way of example and not limitation pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl,
15   piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-
20   quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl,
25   benzoxazolinyl, and isatinoyl.

By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan,
30   tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl,

4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

5   By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically,

10   nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

          "Carbocycle" means a saturated, unsaturated or aromatic ring having 3 to 7 carbon atoms as a monocycle or 7 to 12 carbon atoms as a bicycle. Monocyclic carbocycles have 3 to

15   6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, e.g. arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and

20   naphthyl.

          The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

25

          The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

          "Diastereomer" refers to a stereoisomer with two or more centers of chirality and

30   whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D andthe linkeror R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d andthe linkeror (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R^1" or "R^{6a}", then it will be understood that the groups may be the same or different, i.e., each group is independently selected.

Candidate compounds contain at least one A^1 (which in turn contains 1-3 A^3 groups) but also may contain at least one A^2 group.

A^1 is:
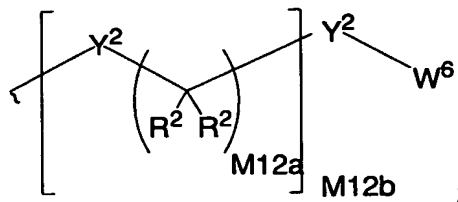
A^2 is:
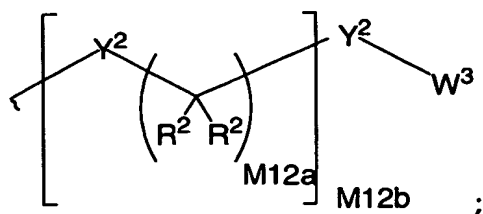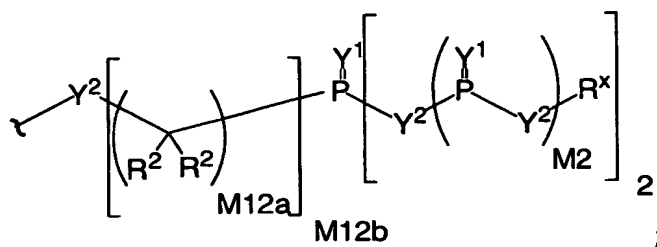
$$Y^2 \left[\left(R^2 R^2 \right)_{M12a} \right]_{M12b} Y^2 - W^3 \quad ;$$

A^3 is:

$$Y^2 \left[\left(R^2 R^2 \right)_{M12a} \right]_{M12b} \overset{\overset{Y^1}{\|}}{P} - Y^2 \left[\overset{\overset{Y^1}{\|}}{P} \left(Y^2 \right) \right]_{M2} R^X \Bigg]_2 \quad ;$$

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)($

$R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)($

$R^x))$, -S(O)$_{M2}$-, or -S(O)$_{M2}$-S(O)$_{M2}$-;

R^x is independently H, R^1, W^3, a protecting group, or the formula:

$$\left[\overset{\overset{Y^1}{\|}}{C} Y^2 \right]_{M1a} \left[\overset{R^y \; R^y}{\underset{|}{C}} \left(Y^2 \right)_{M12c} \right]_{M1c} \left[\overset{\overset{Y^1}{\|}}{C} Y^2 \right]_{M1d} R^y \quad ;$$
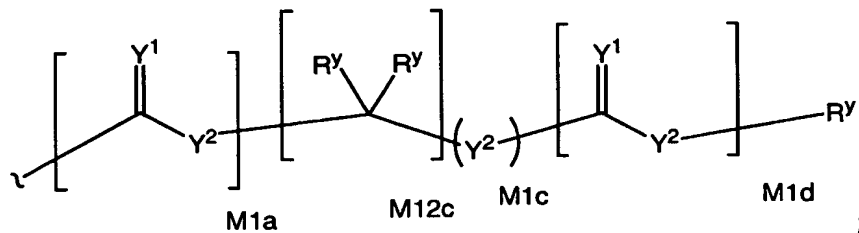
R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or an alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently

substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then

R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or -NO$_2$;

R^{3b} is Y^1;

R^{3c} is -R^x, -N(R^x)(R^x), -SR^x, -S(O)R^x, -S(O)$_2$R^x, -S(O)(OR^x), -S(O)$_2$(OR^x),

-OC(Y')R^x, -OC(Y')OR^x, -OC(Y')(N(R^x)(R^x)), -SC(Y')R^x, -SC(Y')OR^x,

-SC(Y')(N(R^x)(R^x)), -N(R^x)C(Y')R^x, -N(R^x)C(Y')OR^x, or -N(R^x)C(Y')(N(R^x)(R^x)) ;

R^{3d} is -C(Y')R^x, -C(Y')OR^x or -C(Y')(N(R^x)(R^x));

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, -C(Y')R^5, -C(Y')W^5, -SO$_2$$R^5$, or -SO$_2$$W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

W^7 is a heterocycle bonded through a nitrogen atom of said heterocycle and independently substituted with 0, 1 or 2 A^0 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

W^5 carbocycles and W^5 heterocycles may be independently substituted with 0 to 3 R^2 groups. W^5 may be a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. W^5 may have 3 to 10 ring atoms, e.g., 3 to 7 ring atoms. The W^5 rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

A W^5 heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). W^5 heterocyclic monocycles may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). W^5 heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 hetero

atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The W^5 heterocycle may be bonded to Y^2 through a carbon, nitrogen, sulfur or other atom by a stable covalent bond.

W^5 heterocycles include for example, pyridyl, dihydropyridyl isomers, piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl. W^5 also includes, but is not limited to, examples such as:
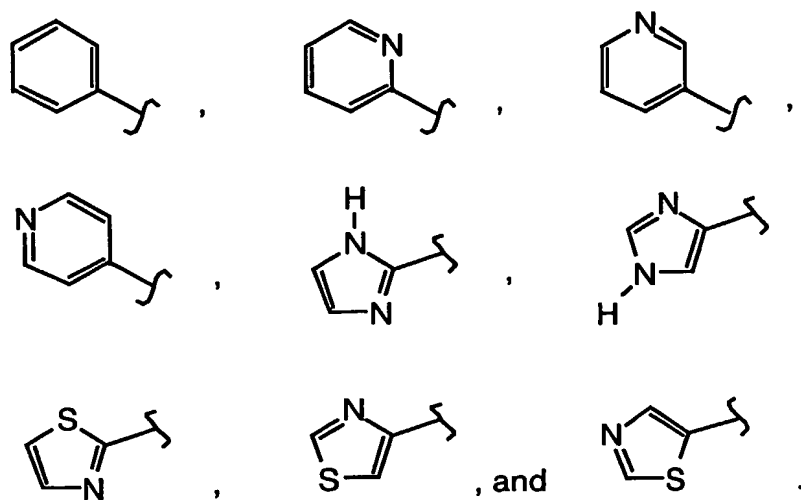
W^5 carbocycles and heterocycles may be independently substituted with 0 to 3 R^2 groups, as defined above. For example, substituted W^5 carbocycles include:
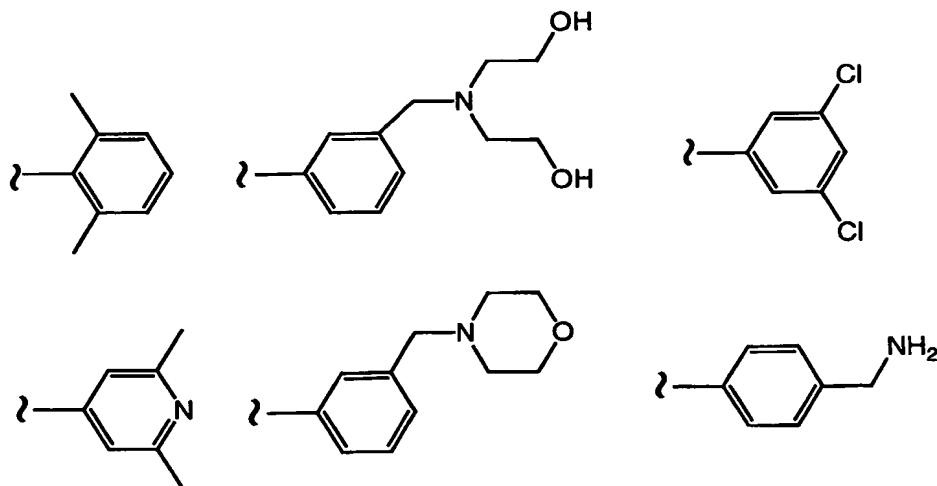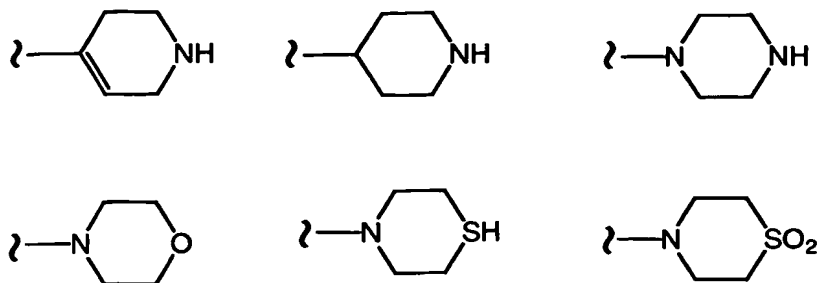
Examples of substituted phenyl carbocycles include:
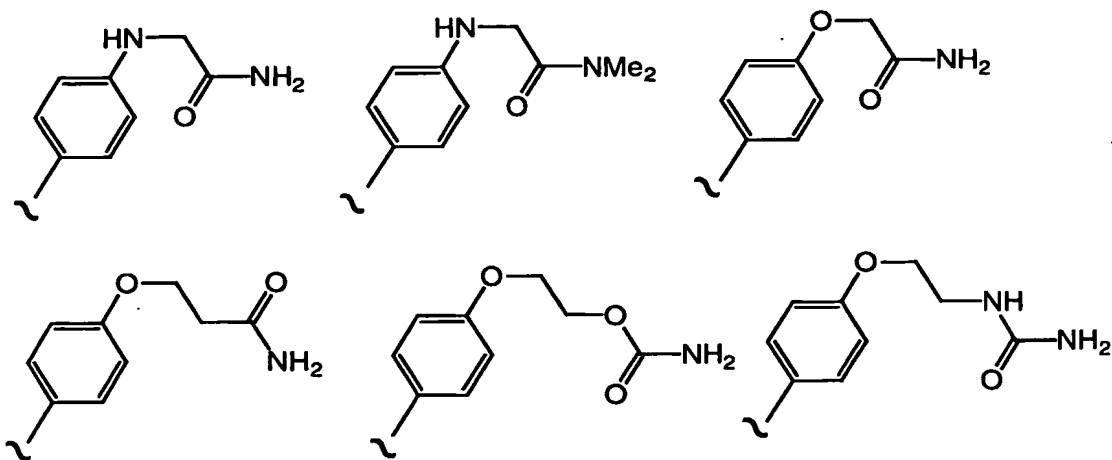
5

Embodiments

The following embodiments represent preferred choices for various substituents found on the candidate compounds of this invention. Each embodiment is to be construed as

10 representing the enumerated substituent (or assembly of substituents) in combination with each and every other substituent that is not enumerated in the embodiment. For example, if W^3 is specified in an embodiment, then W^3 is locked but the remaining substituents can be set in any combination possible within the definition of A^3.

In an embodiment A^1 is
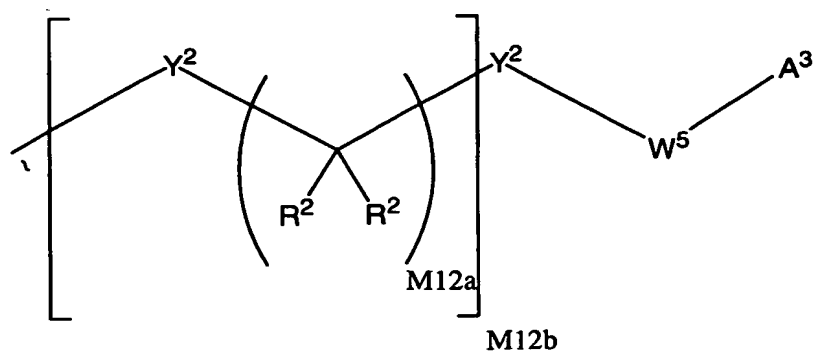
In an embodiment A^1 is
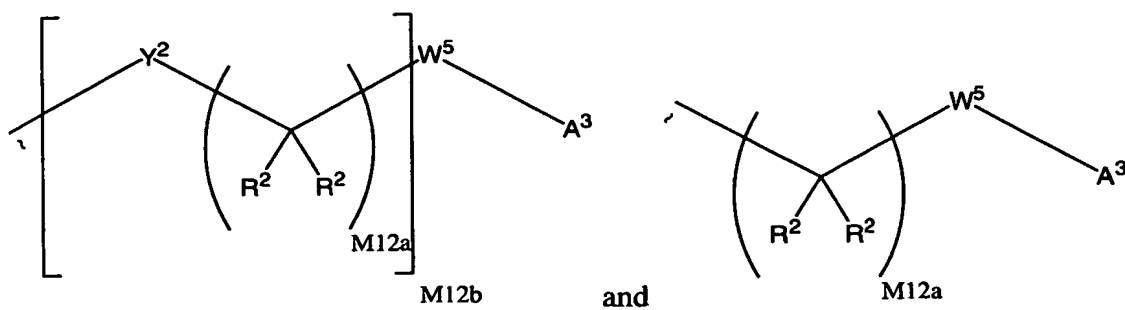
An embodiment of A^3 includes where M2 is 0, such as:
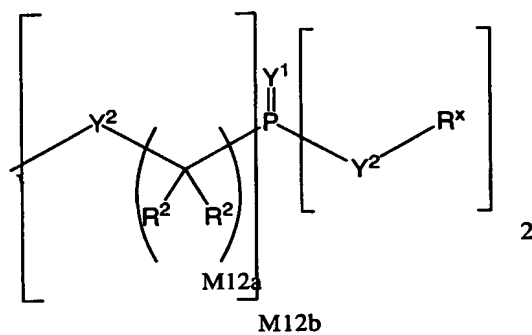
and where M12b is 1, Y^1 is oxygen, and Y^{2b} is oxygen (O) or nitrogen (N(R^x)) such as:
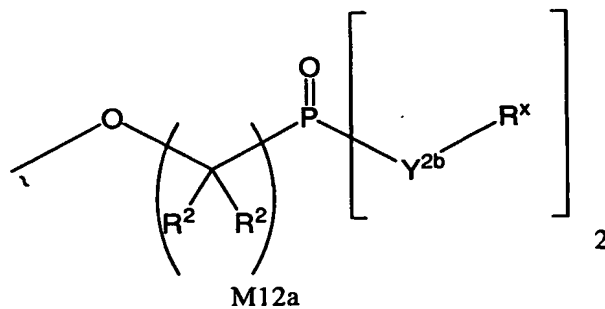
Another embodiment of A^3 is:

M12b
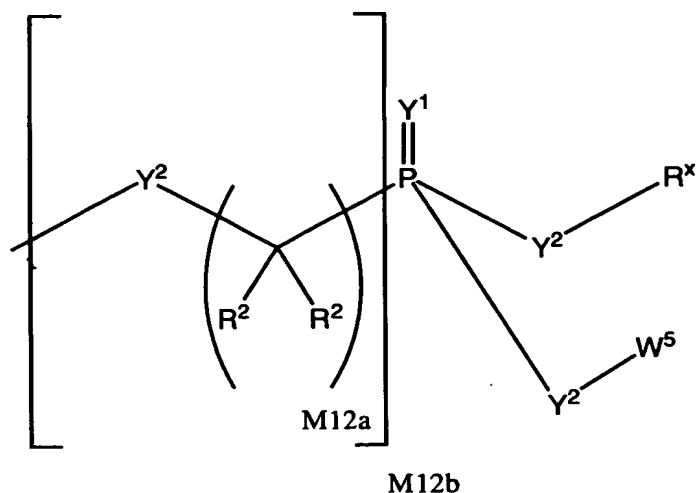
where W^5 is a carbocycle such as phenyl or substituted phenyl. Such embodiments include:
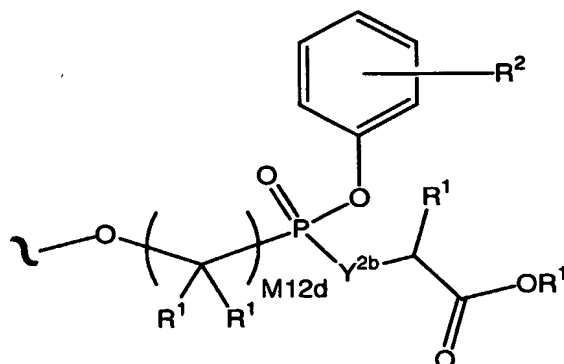
where Y^{2b} is O or $N(R^x)$; M12d is 1, 2, 3, 4, 5, 6, 7 or 8; and the phenyl carbocycle is

substituted with 0 to 3 R^2 groups. Such embodiments of A^3 include phenyl phosphonamidate-

alanate esters and phenyl phosphonate-lactate esters:

and
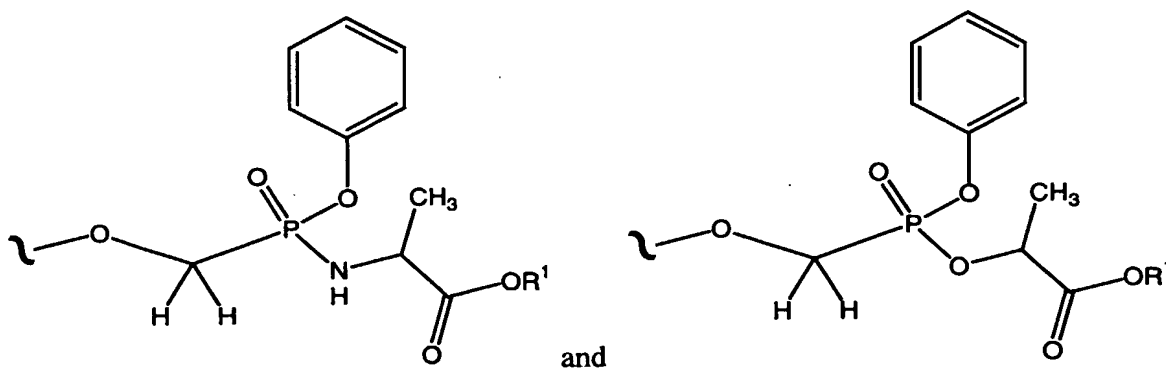
Embodiments of R^x include esters, carbamates, carbonates, thioesters, amides,

thioamides, and urea groups:
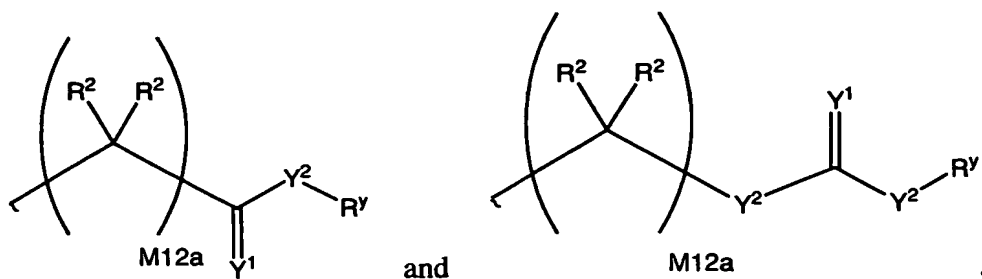
Embodiments of A^2 include where W^3 is W^5, such as:
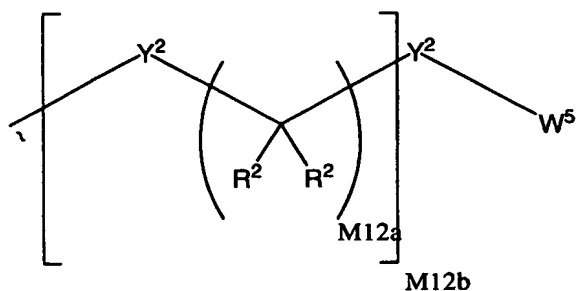
5   Alternatively, A^2 is phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl or substituted pyridyl.

In other embodiments W^4 may be R^4, W^{5a} is a carbocycle or heterocycle and W^{5a} is optionally and independently substituted with 1, 2, or 3 R^2 groups. For example, W^{5a} may be 3,5-dichlorophenyl.

10   An embodiment of A^1 is:
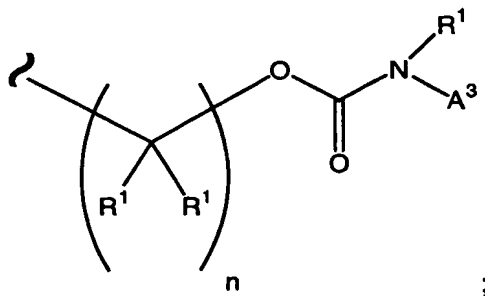
n is an integer from 1 to 18;

An embodiment of A^3 optionally is of the formula:

M12a   ;
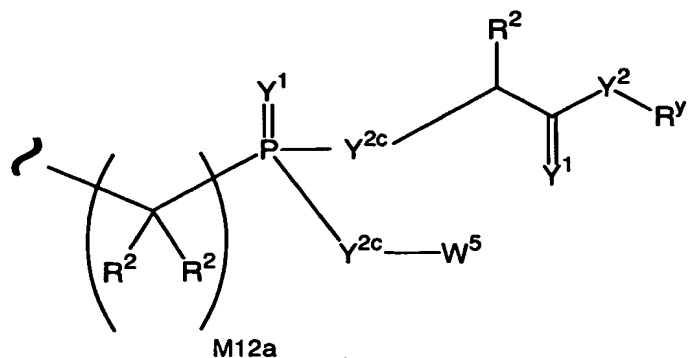
and Y^{2c} is O, $N(R^y)$ or S. For example, R^1 may be H and n may be 1.

An embodiment of A^1 optionally comprises a phosphonate group attached to an imidazole nitrogen through a heterocycle linker, such as:

M12d   ;

and
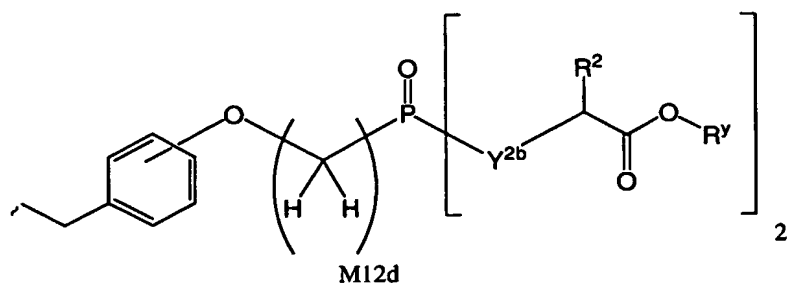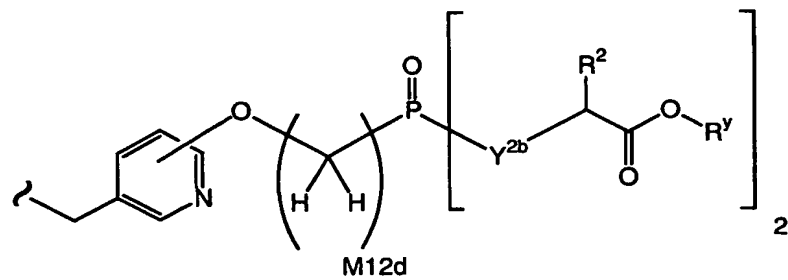
M12d   ;

where Y^{2b} is O or $N(R^2)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8. The A^3 unit may be attached at any of the W^5 carbocycle or heterocycle ring atoms, e.g. ortho, meta, or para on a disubstituted W^5.

A_1 optionally is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-W_3$, and W_3 is substituted with 1 to 3 A_3 groups.

A_2 optionally is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-W_3$.

A_3 optionally is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-P(Y_1)(Y_1R_{6a})(Y_1R_{6a})$.

X_2 and X_3 optionally are independently a bond, -O-, $-N(R_2)-$, $-N(OR_2)-$, $-N(N(R_2)(R_2))-$, -S-, -SO-, or $-SO_2-$.

Each Y_1 optionally is independently O, $N(R_2)$, $N(OR_2)$, or $N(N(R_2)(R_2))$, wherein each Y_1 is bound by two single bonds or one double bond.

R_1 optionally is independently H or alkyl of 1 to 12 carbon atoms.

R_2 optionally is independently H, R_3 or R_4 wherein each R_4 is independently substituted with 0 to 3 R_3 groups.

R_3 optionally is independently F, Cl, Br, I, -CN, N_3, $-NO_2$, $-OR_{6a}$, $-OR_1$, $-N(R_1)_2$, $-N(R_1)(R_{6b})$, $-N(R_{6b})_2$, $-SR_1$, $-SR_{6a}$, $-S(O)R_1$, $-S(O)_2R_1$, $-S(O)OR_1$, $-S(O)OR_{6a}$, $-S(O)_2OR_1$, $-S(O)_2OR_{6a}$, $-C(O)OR_1$, $-C(O)R_{6c}$, $-C(O)OR_{6a}$, $-OC(O)R_1$, $-N(R_1)(C(O)R_1)$, $-N(R_{6b})(C(O)R_1)$, $-N(R_1)(C(O)OR_1)$, $-N(R_{6b})(C(O)OR_1)$, $-C(O)N(R_1)_2$, $-C(O)N(R_{6b})(R_1)$, $-C(O)N(R_{6b})_2$, $-C(NR_1)(N(R_1)_2)$, $-C(N(R_{6b}))(N(R_1)_2)$, $-C(N(R_1))(N(R_1)(R_{6b}))$, $-C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-C(N(R_1))(N(R_{6b})_2)$, $-C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_1)C(N(R_1))(N(R_1)_2)$, $-N(R_1)C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_1))(N(R_1)_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)_2)$, $-N(R_{6b})C(N(R_1))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_1)C(N(R_1))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_1)(R_{6b}))$, $-N(R_{6b})C(N(R_1))(N(R_{6b})_2)$, $-N(R_1)C(N(R_{6b}))(N(R_{6b})_2)$, $-N(R_{6b})C(N(R_{6b}))(N(R_{6b})_2)$, =O, =S, $=N(R_1)$, $=N(R_{6b})$ or W_5.

R_4 optionally is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms.

R_5 optionally is independently R_4 wherein each R_4 is substituted with 0 to 3 R_3 groups; or R_5 is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R_3 groups.

R_{6a} is independently H or an ether- or ester-forming group.

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound.

R_{6c} is independently H or the residue of an amino-containing compound.

W_4 is R_5, $-C(Y_1)R_5$, $-C(Y_1)W_5$, $-SO_2R_5$, or $-SO_2W_5$.

W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups.

m1 is independently an integer from 0 to 12, wherein the sum of all m1's within each individual embodiment of A_1, A_2 or A_3 is 12 or less.

m2 is independently an integer from 0 to 2.

In another embodiment A_1 is $-(C(R_2)(R_2))_{m1}-W_3$, wherein W_3 is substituted with 1

A_3 group, A_2 is $-(C(R_2)(R_2))_{m1}-W_3$, and A_3 is $-(C(R_2)(R_2))_{m1}P(Y_1)(Y_1R_{6a})(Y_1R_{6a})$.
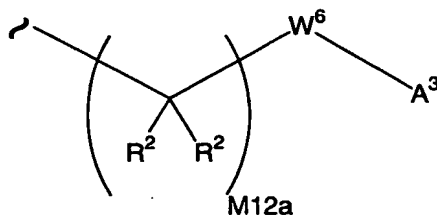
In an embodiment A^1 is of the formula:

5
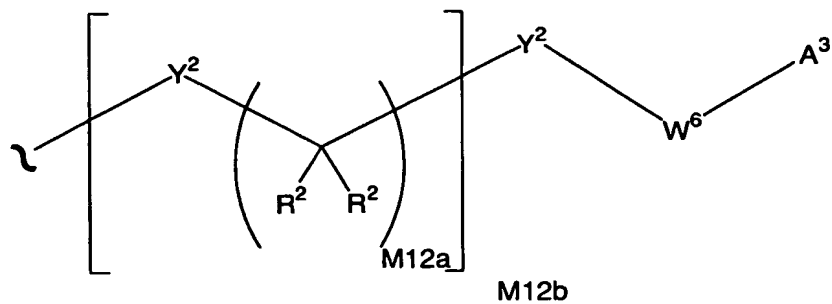
In an embodiment A^1 is of the formula:
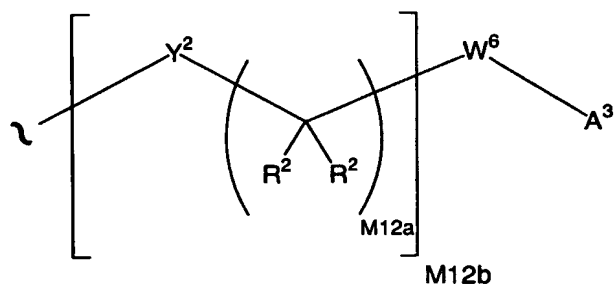
In an embodiment A^1 is of the formula:

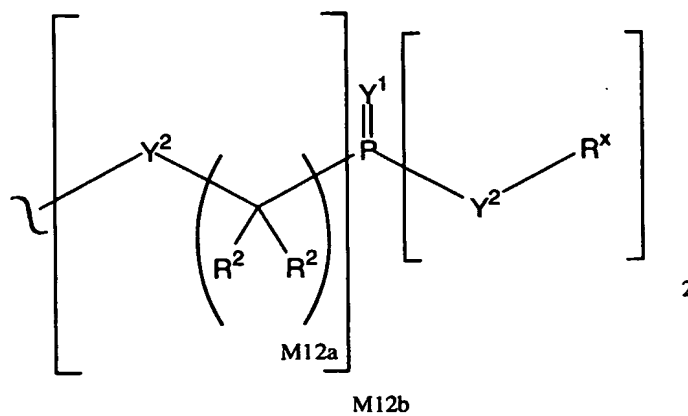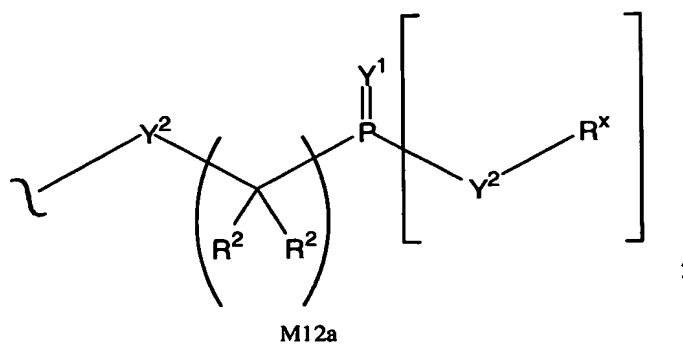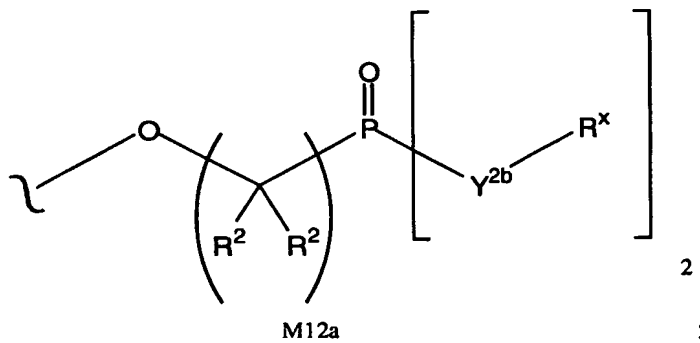

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In an embodiment A^1 is of the formula:
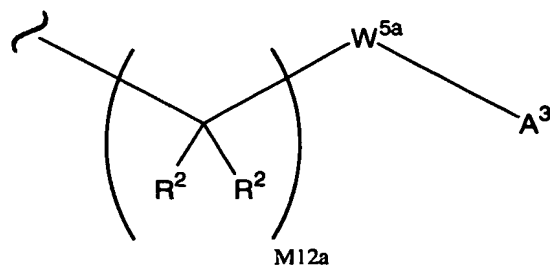
;

and W^{5a} is a carbocycle or a heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups.

In an embodiment M12a is 1.

5

In an embodiment A^3 is of the formula:

M12b

In an embodiment A^3 is of the formula:

M12a

10

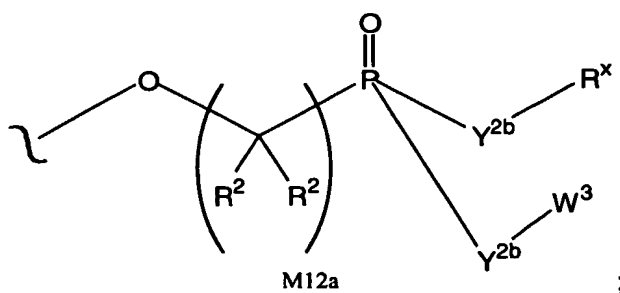In an embodiment A^3 is of the formula:

M12a

Y^{1a} is O or S; and

Y^{2a} is O, N(R^x) or S.

In an embodiment A^3 is of the formula:

M12a

and Y^{2b} is O or N(R^x).

In an embodiment A^3 is of the formula:

M12d

Y^{2b} is O or N(R^x); and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In and embodiment A^3 is of the formula:

M12d

Y^{2b} is O or N(R^x); and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment M12d is 1.

In an embodiment A^3 is of the formula:

M12b

In an embodiment A^3 is of the formula:

M12b

In an embodiment W^5 is a carbocycle.

In an embodiment A^3 is of the formula:
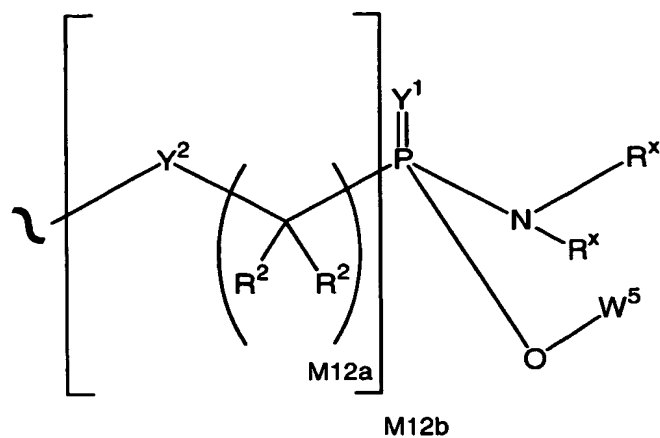
M12b

In an embodiment W^5 is phenyl.

In an embodiment M12b is 1.

In and embodiment A^3 is of the formula:
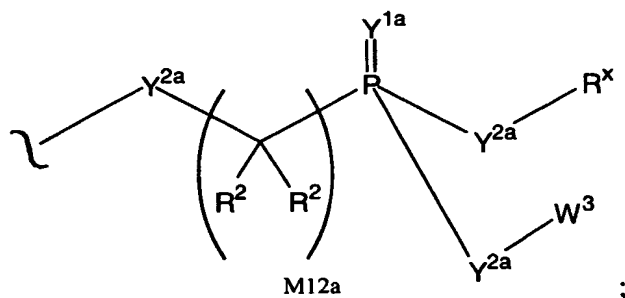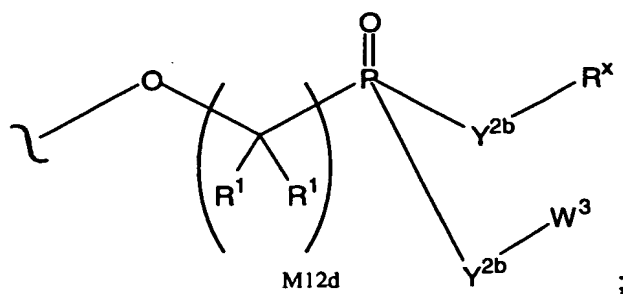

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^x)$ or S.

In an embodiment A^3 is of the formula:

and Y^{2b} is O or $N(R^x)$.

In an embodiment A^3 is of the formula:
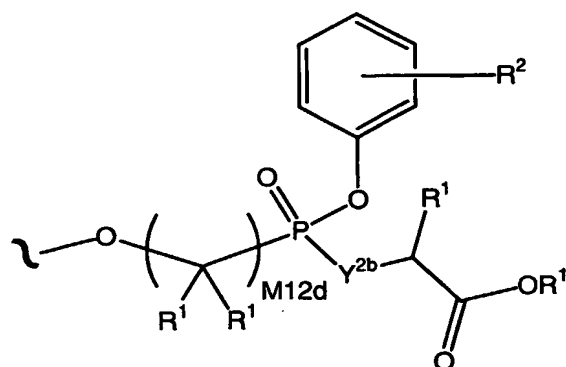
Y^{2b} is O or $N(R^x)$; and

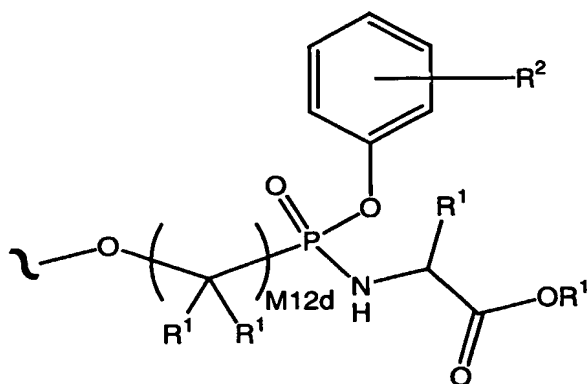M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment R^1 is H.

In an embodiment M12d is 1.

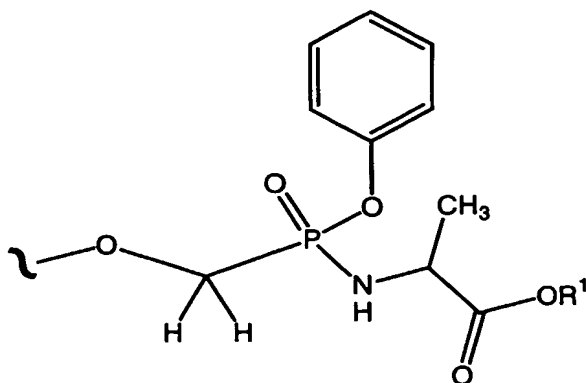In an embodiment A^3 is of the formula:

wherein the phenyl carbocycle is substituted with 0 to 3 R^2 groups.
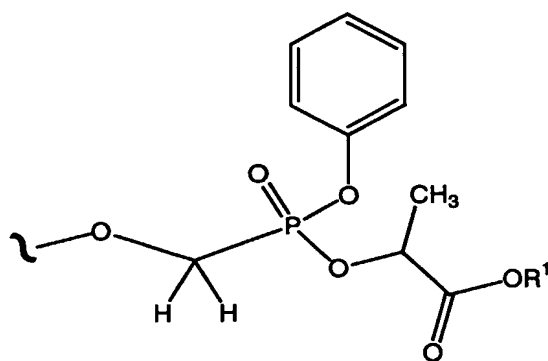
In an embodiment A^3 is of the formula:
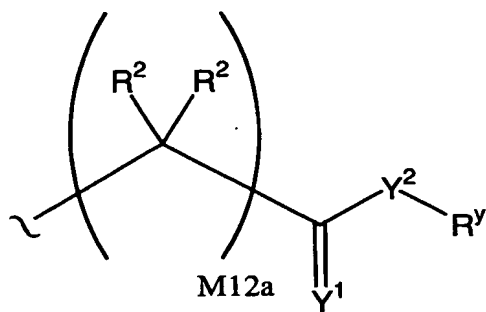
In an embodiment A^3 is of the formula:
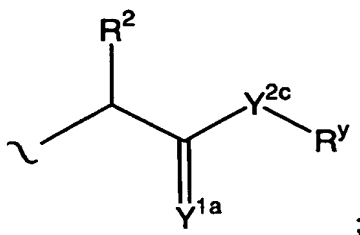
In an embodiment A^3 is of the formula:

In an embodiment R^x is of the formula:

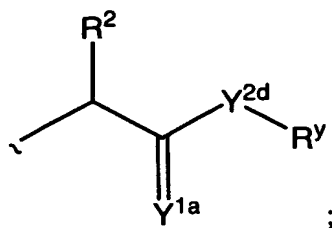In an embodiment R^x is of the formula:

Y^{1a} is O or S; and

Y^{2c} is O, $N(R^y)$ or S.

In an embodiment R^x is of the formula:

Y^{1a} is O or S; and

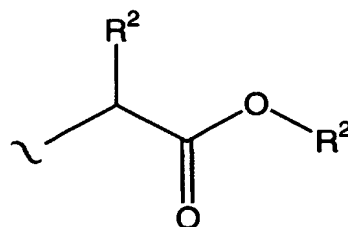Y^{2d} is O or $N(R^y)$.

In an embodiment R^x is of the formula:

In an embodiment R^x is of the formula:

In an embodiment R^x is of the formula:

In an embodiment A^3 is of the formula:

In an embodiment A^3 is of the formula:

M12a

; and

R^x is of the formula:

M12a

.

In an embodiment A^3 is of the formula:

M12a

;

Y^{1a} is O or S; and

Y^{2a} is O, N(R^2) or S.

In an embodiment A^3 is of the formula:

M12a

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

In an embodiment A^3 is of the formula:

M12d

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^3 is of the formula:

M12d

Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^3 is of the formula:

$$
\left[\underset{H\;\;H}{\overset{O}{\underset{\|}{\smile O-\text{P}}}}-Y^{2b}-\overset{R^2}{\underset{\underset{O}{\|}}{C}}-O-R^2 \right]_2
$$

and Y^{2b} is O or $N(R^2)$.

In an embodiment A^3 is of the formula:

$$
\left[\overset{O}{\underset{H\;\;H}{\overset{\|}{\smile O-\text{P}}}}-O-\underset{\underset{O}{\|}}{C}-O-R^2 \right]_2 .
$$

In an embodiment A^3 is of the formula:

$$
\underset{M12a}{\smile Y^2 \left(\underset{R^2\;\;R^2}{} \right) \overset{\overset{Y^1}{\|}}{P} \left\langle \begin{array}{l} R^x \\ Y^2 \\ Y^2-W^3 \end{array} \right.} \quad ; \text{ and}
$$

R^x is of the formula:

$$
\smile \left(\underset{M12a}{\underset{R^2\;\;R^2}{}} \right) \underset{\underset{Y^1}{\|}}{C} Y^2 - R^y
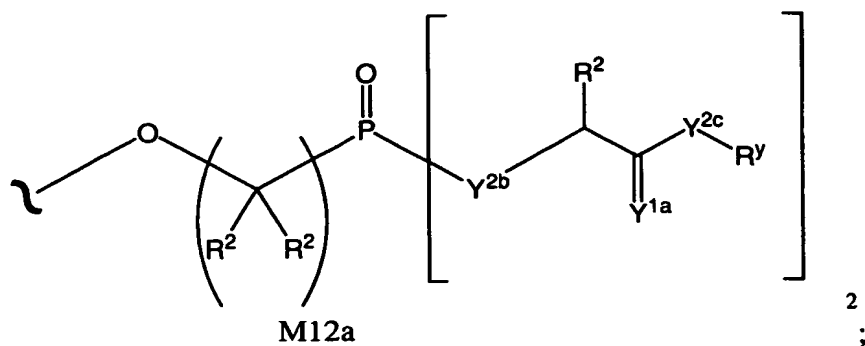$$

.

In an embodiment A^3 is of the formula:

;

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^2)$ or S.

In an embodiment A^3 is of the formula:

;

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

In an embodiment A^3 is of the formula:

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^3 is of the formula:

Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^3 is of the formula:

and Y^{2b} is O or $N(R^2)$.

In an embodiment A^1 is of the formula:

; and

A^3 is of the formula:

In an embodiment A^1 is of the formula:

5   A^3 is of the formula:

; and

R^x is of the formula:

In an embodiment A^1 is of the formula:

M12a   ;

A^3 is of the formula:

M12a   2
                                               ;

Y^{1a} is O or S; and

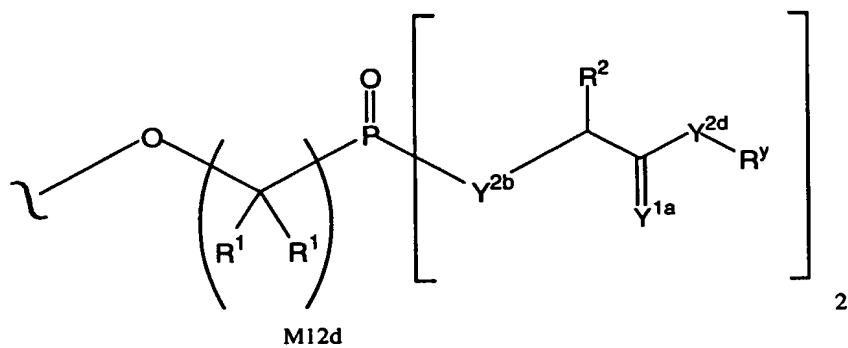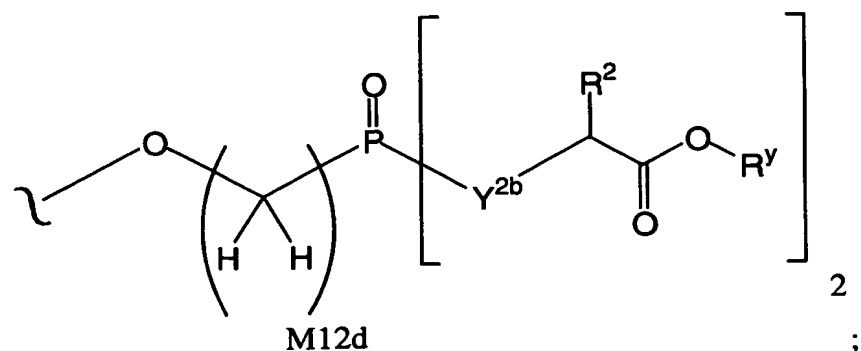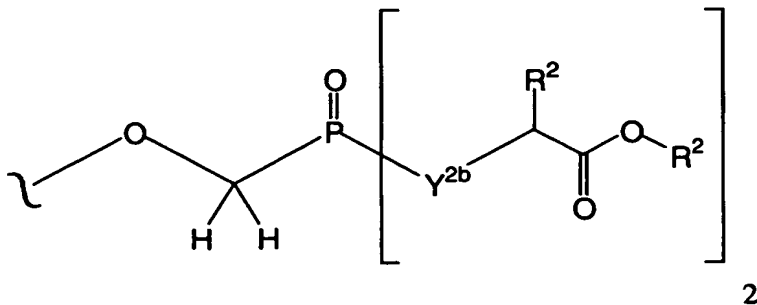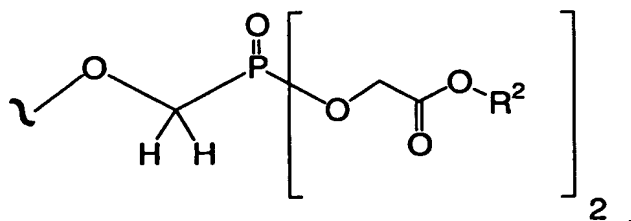Y^{2a} is O, $N(R^2)$ or S.

In an embodiment A^1 is of the formula:

M12a   ;

W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups;

A^3 is of the formula:

M12a

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

In an embodiment A^1 is of the formula:

W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups;

A^3 is of the formula:

M12d

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^1 is of the formula:

M12d

Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.
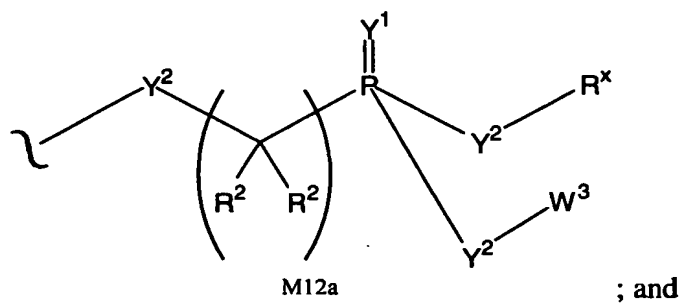
In an embodiment A^1 is of the formula:

M12b   ; and

A^3 is of the formula:

M12b   .

In an embodiment A^1 is of the formula:

$$\left[\begin{array}{c} \xi\text{---}Y^2\left(\begin{array}{c} \\ R^2 \quad R^2 \end{array}\right)_{\text{M12a}}W^5\text{---}A^3 \end{array} \right]_{\text{M12b}} ;$$

A^3 is of the formula:

$$\xi\text{---}Y^2\left(\begin{array}{c} \\ R^2 \quad R^2 \end{array}\right)_{\text{M12a}}\overset{\overset{Y^1}{\|}}{P}\begin{array}{c} \text{---}Y^2\text{---}R^x \\ \text{---}Y^2\text{---}W^3 \end{array} ; \text{ and}$$

5

R^x is of the formula:

$$\xi\left(\begin{array}{c} R^2 \quad R^2 \\ \\ \end{array}\right)_{\text{M12a}}\overset{\underset{\|}{Y^1}}{C}\text{---}Y^2\text{---}R^y .$$

In an embodiment A^1 is of the formula:

$$\xi\left(\begin{array}{c} \\ R^2 \quad R^2 \end{array}\right)_{\text{M12a}}W^5\text{---}A^3 ;$$

10

A^3 is of the formula:

;

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^2)$ or S.

In an embodiment A^1 is of the formula:

;

W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups;

A^3 is of the formula:

;

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

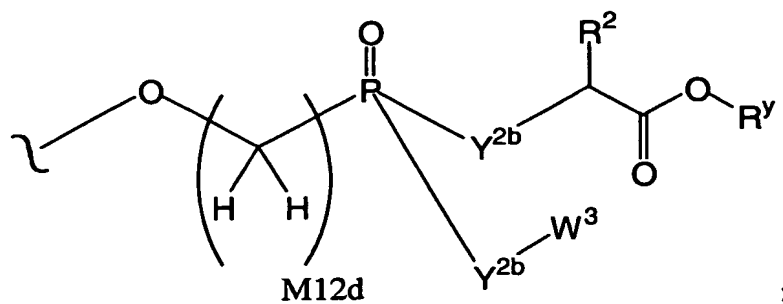Y^{2c} is O, $N(R^y)$ or S.

In an embodiment A^3 is of the formula:

wherein the phenyl carbocycle is substituted with 0 to 3 R^2 groups.

In an embodiment A^1 is of the formula:

W^{5a} is a carbocycle or heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups;

A^3 is of the formula:

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^1 is of the formula:

$$M12d$$
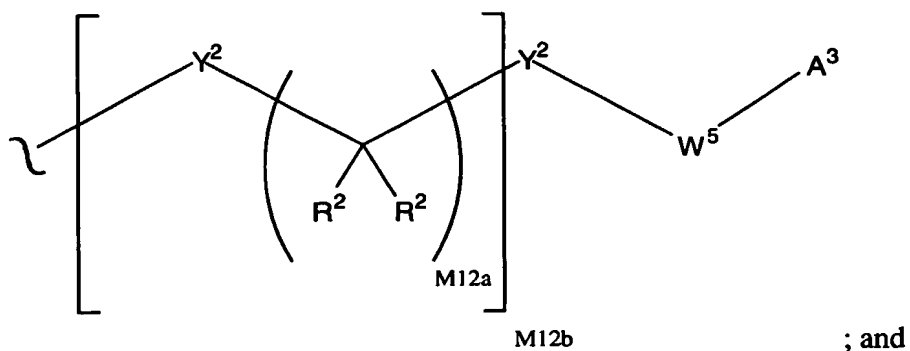
Y^{2b} is O or $N(R^2)$; and
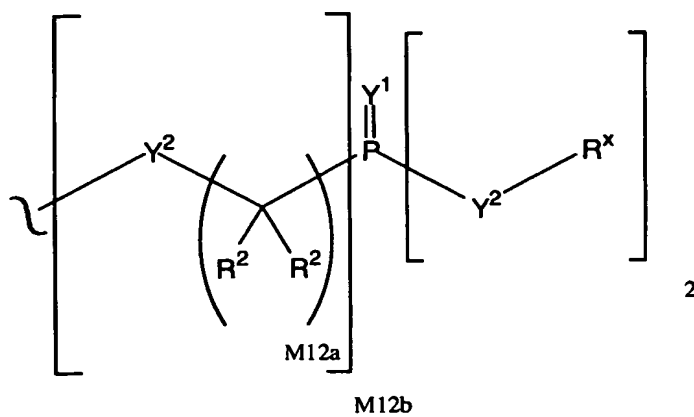
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^2 is of the formula:

$$M12b$$

In an embodiment A^2 is of the formula:

$$M12b.$$

In an embodiment M12b is 1.

In an embodiment M12b is 0, Y^2 is a bond and W^5 is a carbocycle or heterocycle where W^5 is optionally and independently substituted with 1, 2, or 3 R^2 groups.

In an embodiment A^2 is of the formula:
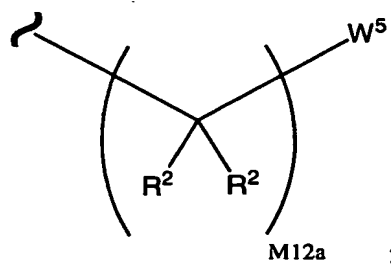
M12a   ;

and W^{5a} is a carbocycle or heterocycle where W^{5a} is optionally and independently

substituted with 1, 2, or 3 R^2 groups.

In an embodiment M12a is 1.

In an embodiment A^2 is selected from phenyl, substituted phenyl, benzyl, substituted

benzyl, pyridyl and substituted pyridyl.

In an embodiment A^2 is of the formula:

M12b

In an embodiment A^2 is of the formula:

M12b.

In an embodiment M12b is 1.

In an embodiment A¹ is of the formula:

$$
\left[Y^2 \left(\underset{R^2}{\overset{}{C}} R^2 \right)_{M12a} W^{3a} \right]_{M12b} A^3 \quad ; \text{ and}
$$

A³ is of the formula:

$$
Y^2 \left(\underset{R^2}{\overset{}{C}} R^2 \right)_{M12a} \overset{\overset{Y^1}{\|}}{P} \left[Y^2 R^x \right]_2 \quad .
$$

In an embodiment A³ is of the formula:

$$
O \overset{\overset{O}{\|}}{\underset{R^2 \; R^2}{C}} P \left[O R^2 \right]_2 \quad .
$$

In an embodiment Rˣ is of the formula:

$$
\left(\underset{}{\overset{R^2 \; R^2}{C}} \right)_{M12a} Y^2 \overset{\overset{Y^1}{\|}}{C} Y^2 - R^y \quad .
$$
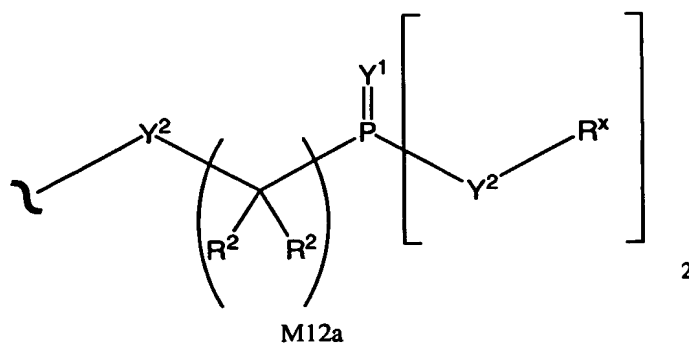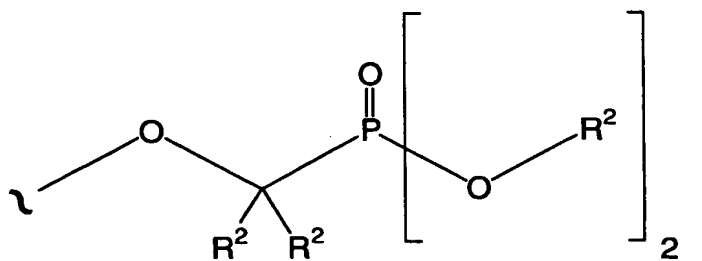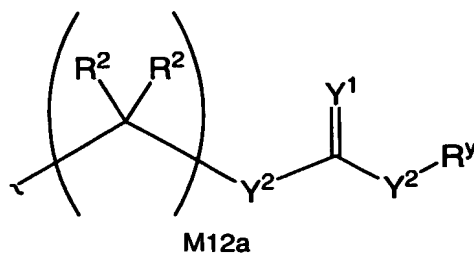
In an embodiment A³ is of the formula:
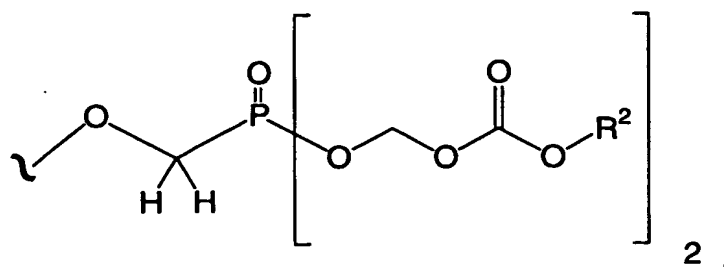
In an embodiment R^x is of the formula:
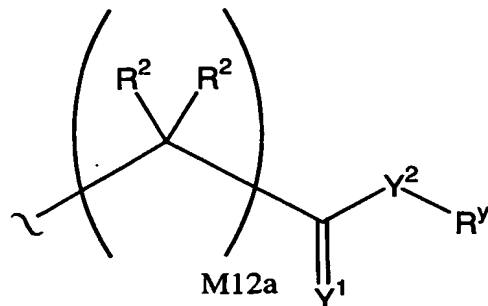
In an embodiment A^3 is of the formula:
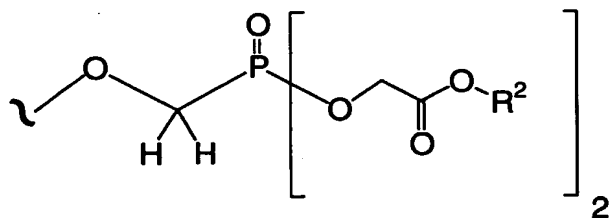
In an embodiment R^4 is isopropyl.

In an embodiment A^1 is of the formula:

A^3 is of the formula:

$$\text{structure with } Y^{1a}, P, Y^{2a}, R^2, R^2, M12a, R^x \text{ (subscript 2)}$$

and Y^{1a} is O or S.

In an embodiment A^3 is of the formula:

$$\text{structure with } Y^{1a}, P, Y^{2a}, R^2, R^2, M12a, Y^{2a}, R^2, Y^1, Y^2, R^y \text{ (subscript 2)}$$

and Y^{2a} is O, $N(R^2)$ or S.

In an embodiment A^3 is of the formula:

$$\text{structure with O, P, R^2, R^2, M12a, Y^{2b}, R^2, Y^{1a}, Y^{2c}, R^y \text{ (subscript 2)}}$$

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

In an embodiment A^3 is of the formula:
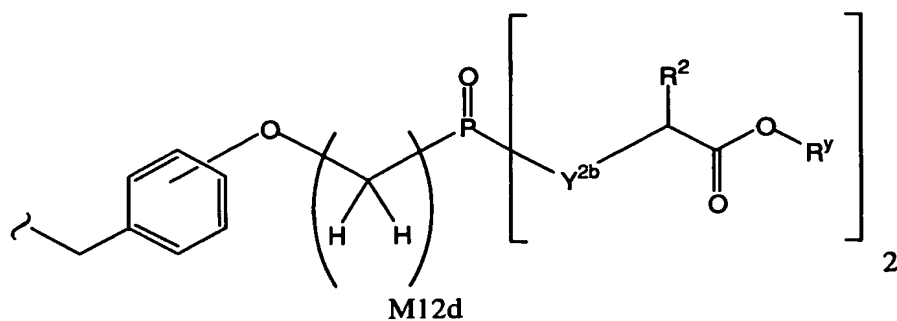
- 51 -

Y^{1a} is O or S;

Y^{2b} is O or N(R^2);

Y^{2d} is O or N(R^y); and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

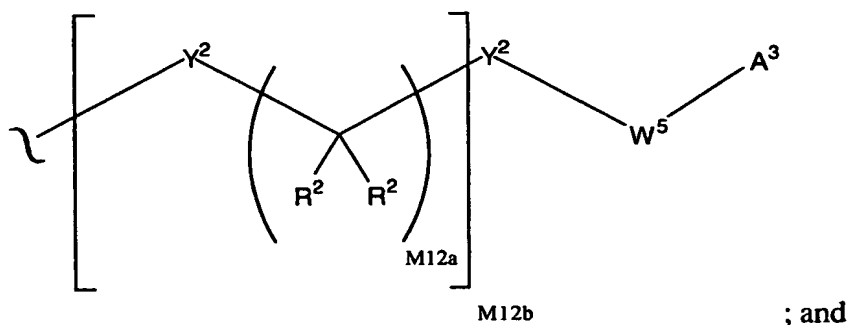In an embodiment A^1 is of the formula:
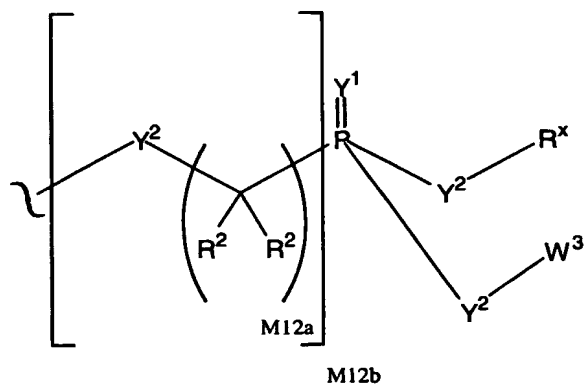

Y^{2b} is O or N(R^2); and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.
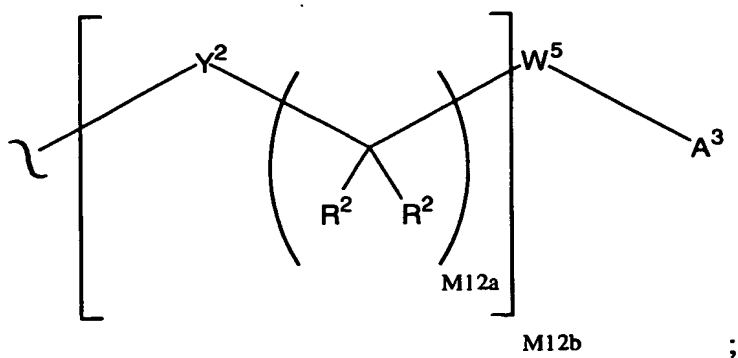
In an embodiment A^1 is of the formula:

and Y^{2b} is O or N(R^2); and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^1 is of the formula:

n is an integer from 1 to 18; A^3 is of the formula:
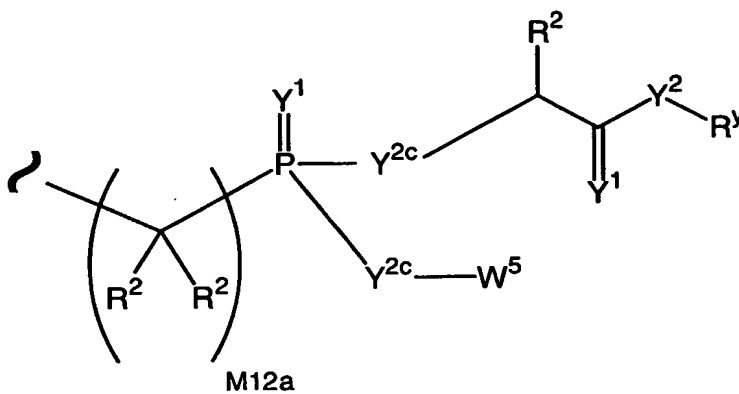
and Y^{2c} is O, $N(R^y)$ or S.

In an embodiment R^1 is H and n is 1.

In an embodiment A^1 is of the formula:
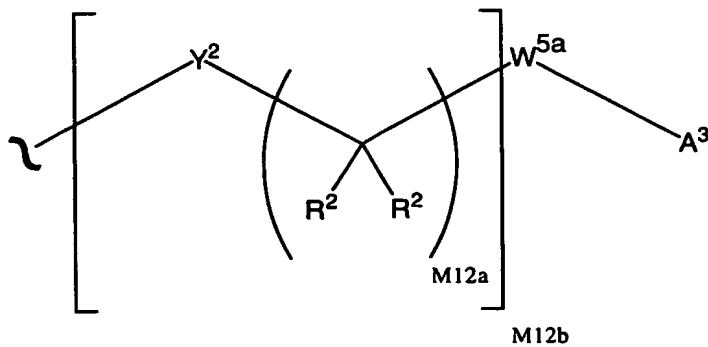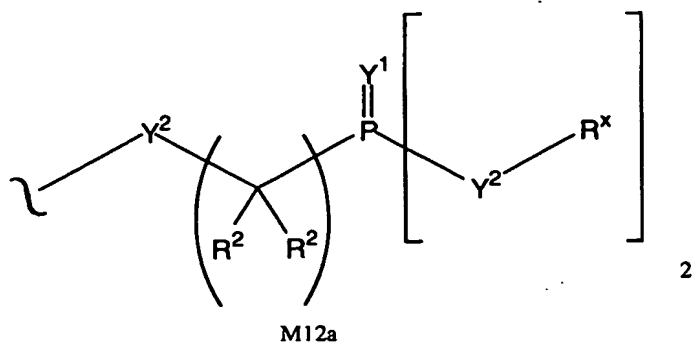
; and

A^3 is of the formula:

$$
\begin{array}{c}
\left[\text{—} Y^2 \left(\underset{R^2 \;\; R^2}{C} \right) \underset{\underset{P}{\parallel}}{\overset{Y^1}{P}} \; Y^2 \text{—} R^x \right]_2 \\
M12a
\end{array}
$$

In an embodiment A^3 is of the formula:

$$
\left[\text{—} O \underset{R^2 \;\; R^2}{C} \underset{\underset{P}{\parallel}}{\overset{O}{P}} O \text{—} R^2 \right]_2 .
$$

In an embodiment R^x is of the formula:

$$
\begin{array}{c}
\text{—} \left(\underset{}{\overset{R^2 \;\; R^2}{C}} \right) Y^2 \underset{\underset{Y^2}{\parallel}}{\overset{Y^1}{C}} Y^2 \text{—} R^y \\
M12a
\end{array}
$$

In an embodiment A^3 is of the formula:

$$
\left[\text{—} O \underset{H \;\; H}{C} \underset{\underset{P}{\parallel}}{\overset{O}{P}} O \text{—} O \underset{\underset{\parallel}{\overset{O}{C}}}{} O \text{—} R^2 \right]_2 .
$$
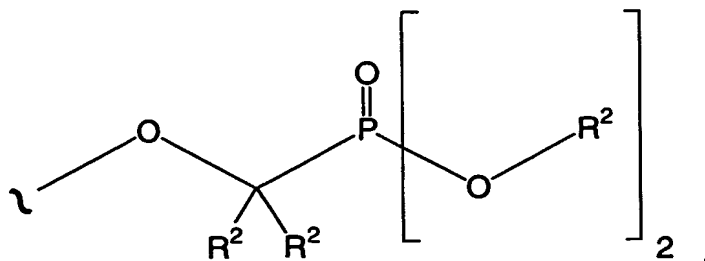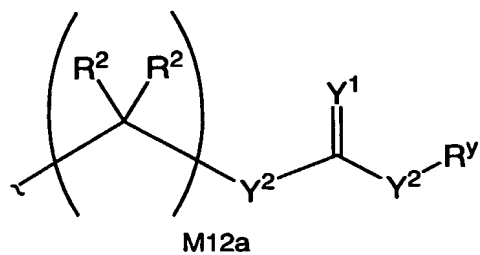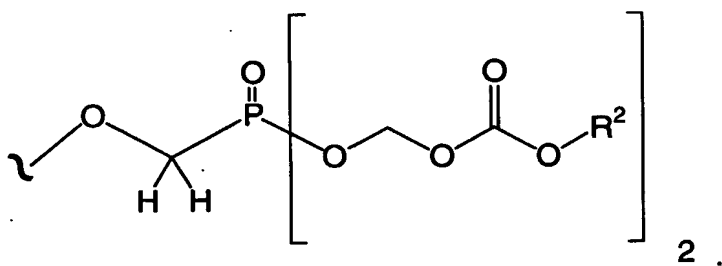
In an embodiment R^x is of the formula:
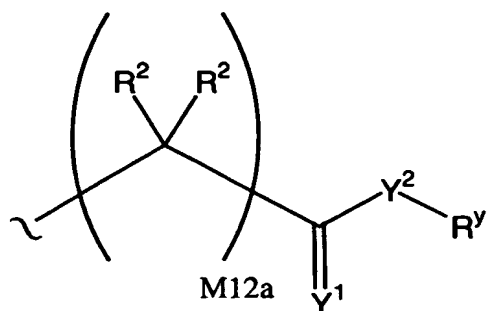
In an embodiment A^3 is of the formula:
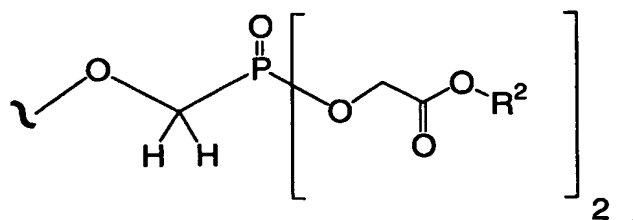
In an embodiment A^2 is selected from:
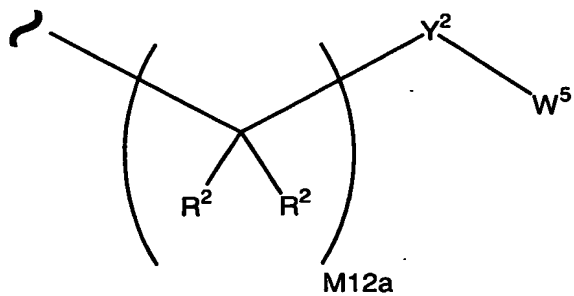
, Y^2-W^5 and W^5,

where W^5 is a carbocycle or a heterocycle and where W^5 is independently substituted with 0 to 3 R^2 groups.
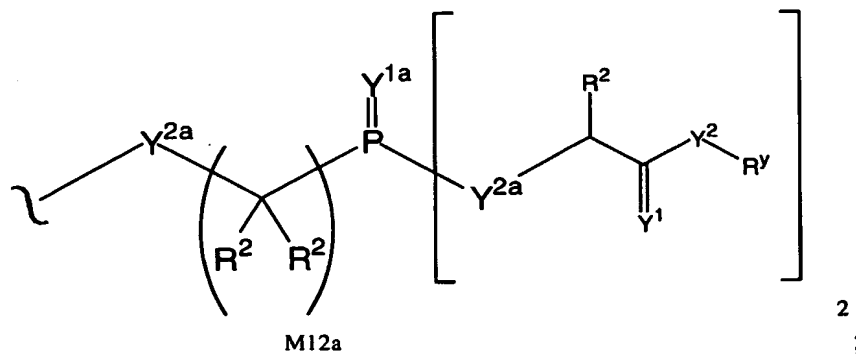
In an embodiment A^3 is of the formula:

and Y^{2a} is O, $N(R^2)$ or S.

In an embodiment A^3 is of the formula:

and Y^{2c} is O, N(R^y) or S.

In an embodiment A^1 is of the formula:

5
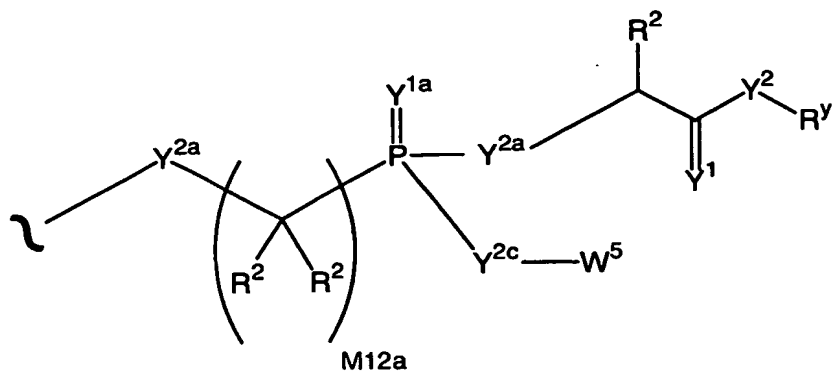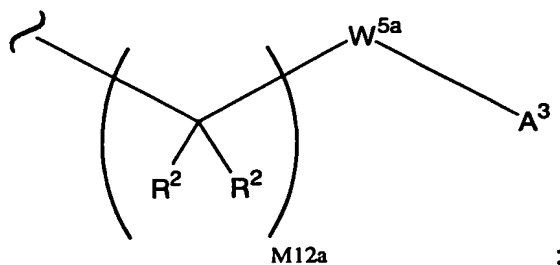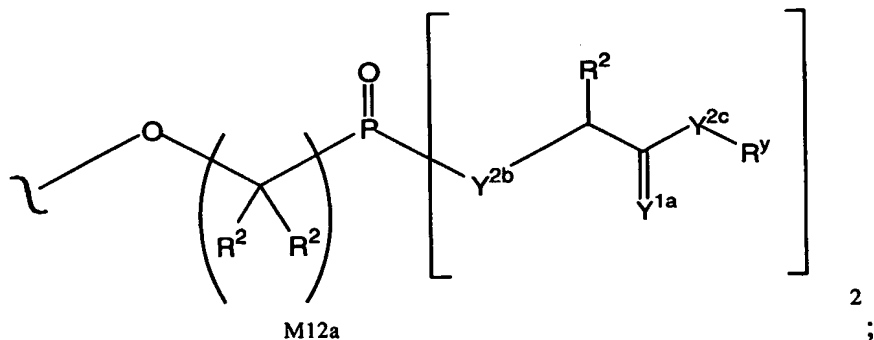
A^3 is of the formula:

W^{5a} is a carbocycle or a heterocycle where the carbocycle or heterocycle is independently substituted with 0 to 3 R^2 groups;

10   Y^{2b} is O or N(R^2); and

Y^{2c} is O, N(R^y) or S.
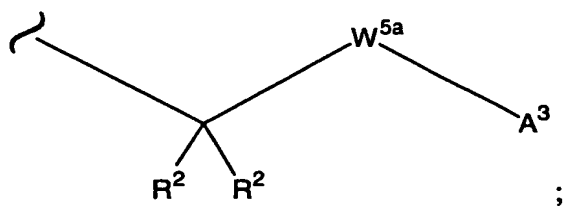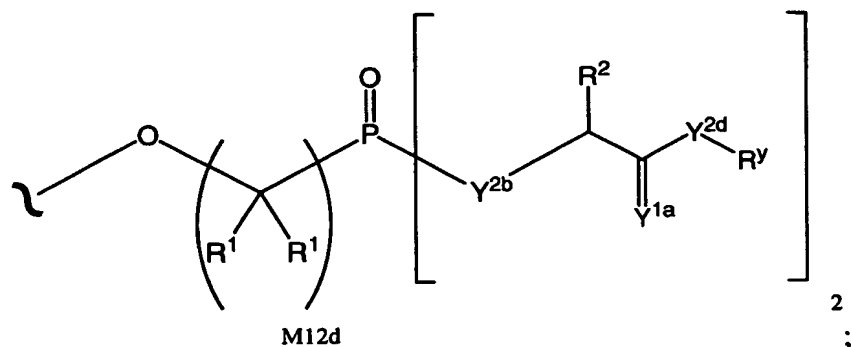
In an embodiment A^1 is of the formula:
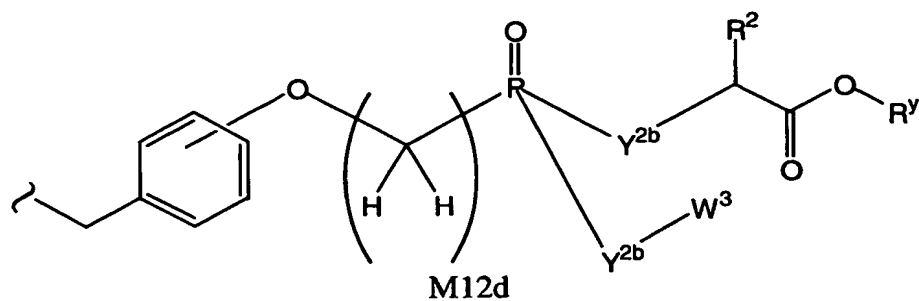
A^3 is of the formula:

Y^{1a} is O or S;

Y^{2b} is O or N(R^2);

Y^{2d} is O or N(R^y); and

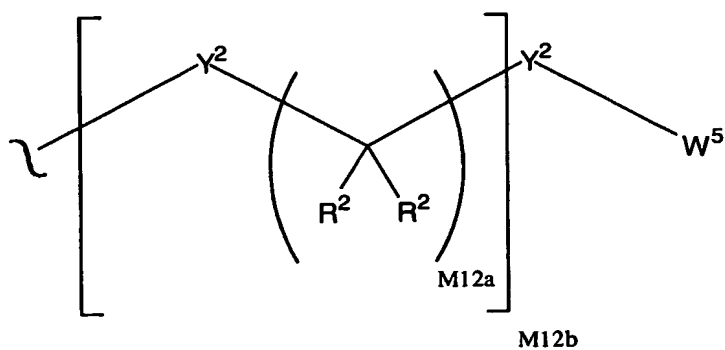M12d is 1, 2, 3, 4, 5, 6, 7 or 8.
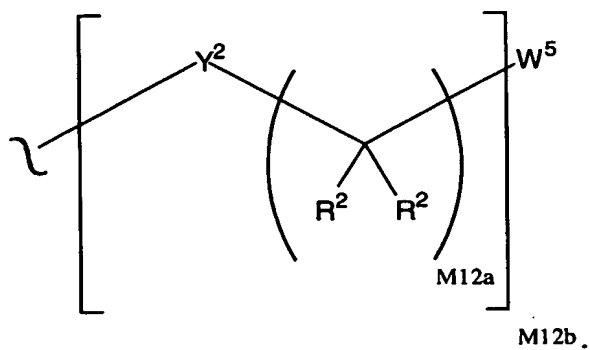
In an embodiment A^1 is of the formula:

Y^{2b} is O or N(R^2); and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^1 is of the formula:

$$\text{M12d}$$

$$\Bigg]_2 \quad ;$$
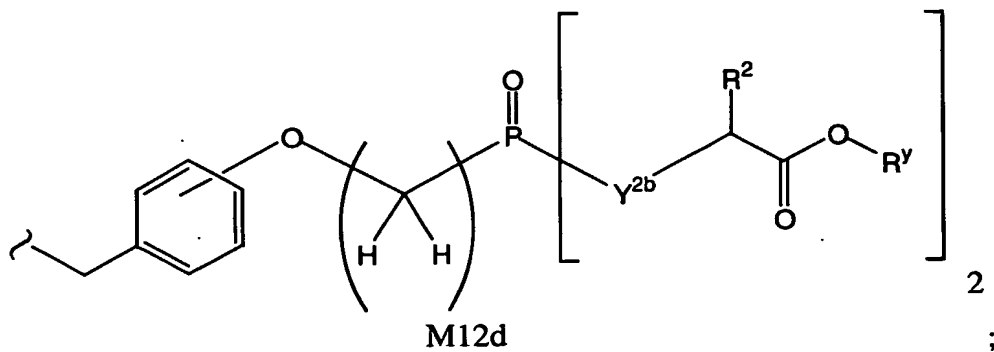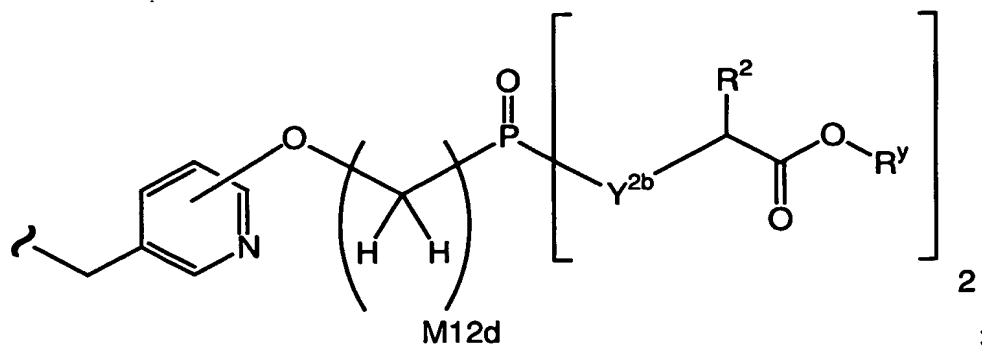
and Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In an embodiment A^2 is a phenyl substituted with 0 to 3 R^2 groups.

In an embodiment W^4 is of the formula:
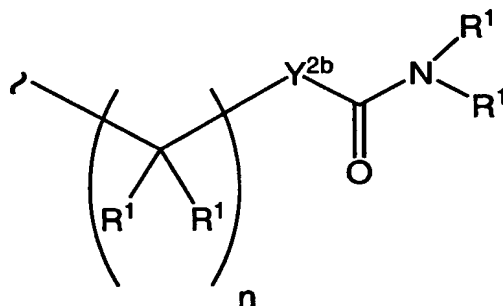
wherein n is an integer from 1 to 18; and Y^{2b} is O or $N(R^2)$.

In an embodiment

A_1 is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-W_3$, wherein W_3 is substituted with 1 to 3 A_3 groups;

A_2 is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-W_3$;

A_3 is $-(X_2-(C(R_2)(R_2))_{m1}-X_3)_{m1}-P(Y_1)(Y_1R_{6a})(Y_1R_{6a})$;

X_2 and X_3 are independently a bond, -O-, $-N(R_2)-$, $-N(OR_2)-$, $-N(N(R_2)(R_2))-$, -S-, -SO-, or -SO2-;

each Y_1 is independently O, $N(R_2)$, $N(OR_2)$, or $N(N(R_2)(R_2))$, wherein each Y_1 is bound by two single bonds or one double bond;

R_1 is independently H or alkyl of 1 to 12 carbon atoms;

R_2 is independently H, R_3 or R_4 wherein each R_4 is independently substituted with 0 to 3 R_3 groups;

R_3 is independently F, Cl, Br, I, -CN, N_3, -NO_2, -OR_{6a}, -OR_1, -$N(R_1)_2$, -$N(R_1)(R_{6b})$, -$N(R_{6b})_2$, -SR_1, -SR_{6a}, -$S(O)R_1$, -$S(O)_2R_1$, -$S(O)OR_1$, -$S(O)OR_{6a}$, -$S(O)_2OR_1$, -$S(O)_2OR_{6a}$, -$C(O)OR_1$, -$C(O)R_{6c}$, -$C(O)OR_{6a}$, -$OC(O)R_1$, -$N(R_1)(C(O)R_1)$, -$N(R_{6b})(C(O)R_1)$, -$N(R_1)(C(O)OR_1)$, -$N(R_{6b})(C(O)OR_1)$, -$C(O)N(R_1)_2$, -$C(O)N(R_{6b})(R_1)$,

-$C(O)N(R_{6b})_2$, -$C(NR_1)(N(R_1)_2)$, -$C(N(R_{6b}))(N(R_1)_2)$, -$C(N(R_1))(N(R_1)(R_{6b}))$, -$C(N(R_{6b}))(N(R_1)(R_{6b}))$, -$C(N(R_1))(N(R_{6b})_2)$, -$C(N(R_{6b}))(N(R_{6b})_2)$, -$N(R_1)C(N(R_1))(N(R_1)_2)$, -$N(R_1)C(N(R_1))(N(R_1)(R_{6b}))$, -$N(R_1)C(N(R_{6b}))(N(R_1)_2)$, -$N(R_{6b})C(N(R_1))(N(R_1)_2)$, -$N(R_{6b})C(N(R_{6b}))(N(R_1)_2)$, -$N(R_{6b})C(N(R_1))(N(R_1)(R_{6b}))$, -$N(R_1)C(N(R_{6b}))(N(R_1)(R_{6b}))$, -$N(R_1)C(N(R_1))(N(R_{6b})_2)$, -

$N(R_{6b})C(N(R_{6b}))(N(R_1)(R_{6b}))$, -$N(R_{6b})C(N(R_1))(N(R_{6b})_2)$, -$N(R_1)C(N(R_{6b}))(N(R_{6b})_2)$, -$N(R_{6b})C(N(R_{6b}))(N(R_{6b})_2)$, =O, =S, =$N(R_1)$, =$N(R_{6b})$ or W_5;

R_4 is independently alkyl of 1 to 12 carbon atoms, alkenyl of 2 to 12 carbon atoms, or alkynyl of 2 to 12 carbon atoms;

R_5 is independently R_4 wherein each R_4 is substituted with 0 to 3 R_3 groups;

R_{5a} is independently alkylene of 1 to 12 carbon atoms, alkenylene of 2 to 12 carbon atoms, or alkynylene of 2-12 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R_3 groups;

R_{6a} is independently H or an ether- or ester-forming group;

R_{6b} is independently H, a protecting group for amino or the residue of a carboxyl-containing compound;

R_{6c} is independently H or the residue of an amino-containing compound;

W_3 is W_4 or W_5;

W_4 is R_5, -$C(Y_1)R_5$, -$C(Y_1)W_5$, -SO_2R_5, or -SO_2W_5;

W_5 is carbocycle or heterocycle wherein W_5 is independently substituted with 0 to 3 R_2 groups;

m1 is independently an integer from 0 to 12, wherein the sum of all m1's within each individual embodiment of A_1, A_2 or A_3 is 12 or less; and

m2 is independently an integer from 0 to 2.

In an embodiment

A_1 is -$(C(R_2)(R_2))_{m1}$-W_3, wherein W_3 is substituted with 1 A_3 group;

A2 is -(C(R2)(R2))m1-W3; and

A3 is -(C(R2)(R2))m1-P(Y1)(Y1R6a)(Y1R6a).

Protecting Groups

5   The chemical substructure of a protecting group varies widely. One function of a

protecting group is to serve as intermediates in the synthesis of the parental drug substance.

Chemical protecting groups and strategies for protection/deprotection are well known in the

art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley &

Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of

10   certain functional groups, to assist in the efficiency of desired chemical reactions, e.g. making

and breaking chemical bonds in an ordered and planned fashion. Protection of functional

groups of nal group, such as the polarity, lipophilicity (hydrophobicity), and other properties

which can be measured by common analytical tools. Chemically protected intermediates may

themselves be biologically active or inactive. Protected compounds may also exhibit altered,

15   and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular

membranes and resistance to enzymatic degradation or sequestration. In this role, protected

compounds may in themselves exhibit therapeutic activity and need not be limited to the role

of chemical intermediates or precursors. The protecting group need not be physiologically

acceptable upon deprotection, although in general it is more desirable if such products are

20   pharmacologically innocuous.a compound alters other physical properties besides the

reactivity of the protected function.

        In the context of the present invention, embodiments of protecting groups include

prodrug moieties and chemical protecting groups.

25

        Protecting groups are available, commonly known and used, and are optionally used to

prevent side reactions with the protected group during synthetic procedures, i.e. routes or

methods to prepare the compounds of the invention. For the most part the decision as to

which groups to protect, when to do so, and the nature of the chemical protecting group

30   "PRT" will be dependent upon the chemistry of the reaction to be protected against (e.g.,

acidic, basic, oxidative, reductive or other conditions) and the intended direction of the

synthesis. The PRT groups do not need to be, and generally are not, the same if the compound is substituted with multiple PRT. In general, PRT will be used to protect functional groups such as carboxyl, hydroxyl or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield

5   free, deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

        Various functional groups of the compounds of the invention may be protection. For

10   example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) are embodiments of "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are

15   included with amides, discussed below.

        A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-

20   62301-6) ("Greene"). See also Kocienski, Philip J.; "Protecting Groups" (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages

25   155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

<u>Ether- and Ester-forming protecting groups</u>

30   Ester-forming groups include: (1) phosphonate ester-forming groups, such as phosphonamidate esters, phosphorothioate esters, phosphonate esters, and phosphon-bis-amidates; (2) carboxyl ester-forming groups, and (3) sulphur ester-forming groups, such as sulphonate, sulfate, and sulfinate.

The phosphonate moieties of the compounds of the invention may or may not be prodrug moieties, i.e. they may or may be susceptible to hydrolytic or enzymatic cleavage or modification. Certain phosphonate moieties are stable under most or nearly all metabolic

5   conditions. For example, a dialkylphosphonate, where the alkyl groups are two or more carbons, may have appreciable stability *in vivo* due to a slow rate of hydrolysis.

Within the context of phosphonate prodrug moieties, a large number of structurally-diverse prodrugs have been described for phosphonic acids (Freeman and Ross in <u>Progress in</u>

10   <u>Medicinal Chemistry</u> 34: 112-147 (1997) and are included within the scope of the present invention. An exemplary embodiment of a phosphonate ester-forming group is the phenyl carbocycle in substructure A_3 having the formula:
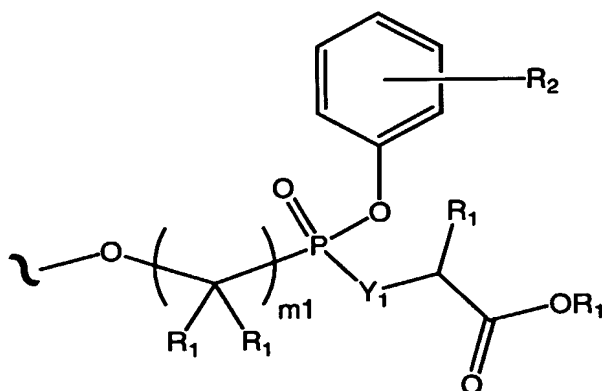
wherein m1 is 1, 2, 3, 4, 5, 6, 7 or 8, and the phenyl carbocycle is substituted with 0

15   to 3 R_2 groups. Also, in this embodiment, where Y_1 is O, a lactate ester is formed. Alternatively , where Y_1 is $N(R_2)$, $N(OR_2)$ or $N(N(R_2)_2$, then phosphonamidate esters result. R_1 may be H or C_1–C_{12} alkyl.

In its ester-forming role, a protecting group typically is bound to any acidic group such

20   as, by way of example and not limitation, a $-CO_2H$ or $-C(S)OH$ group, thereby resulting in - CO_2R^x where R^x is defined herein. Also, R^x for example includes the enumerated ester groups of WO 95/07920.

Examples of protecting groups include:

25   C_3–C_{12} heterocycle (described above) or aryl. These aromatic groups optionally are polycyclic or monocyclic. Examples include phenyl, spiryl, 2- and 3-pyrrolyl, 2- and 3-thienyl,

2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4-
and 5-isothiazolyl, 3- and 4-pyrazolyl, 1-, 2-, 3- and 4-pyridinyl, and 1-, 2-, 4- and 5-
pyrimidinyl, C_3-C_{12} heterocycle or aryl substituted with halo, R^1, R^1-O-C_1-C_{12} alkylene, C_1-
C_{12} alkoxy, CN, NO_2, OH, carboxy, carboxyester, thiol, thioester, C_1-C_{12} haloalkyl (1-6

5   halogen atoms), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl. Such groups include 2-, 3- and 4-
alkoxyphenyl (C_1-C_{12} alkyl), 2-, 3- and 4-methoxyphenyl, 2-, 3- and 4-ethoxyphenyl, 2,3-,
2,4-, 2,5-, 2,6-, 3,4- and 3,5-diethoxyphenyl, 2- and 3-carboethoxy-4-hydroxyphenyl, 2- and
3-ethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-5-hydroxyphenyl, 2- and 3-ethoxy-6-
hydroxyphenyl, 2-, 3- and 4-O-acetylphenyl, 2-, 3- and 4-dimethylaminophenyl, 2-, 3- and 4-

10   methylmercaptophenyl, 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl and 2-,
3- and 4-chlorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-,
2,6-, 3,4- and 3,5-biscarboxyethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxyphenyl,
2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 3,5-
difluorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-

15   trifluoromethylphenyl), 2-, 3- and 4-cyanophenyl, 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-
haloalkylbenzyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylbenzyl and 2-,
3- and 4-trichloromethylphenyl and 2-, 3- and 4-trichloromethylphenyl), 4-N-
methylpiperidinyl, 3-N-methylpiperidinyl, 1-ethylpiperazinyl, benzyl, alkylsalicylphenyl (C_1-C_4
alkyl, including 2-, 3- and 4-ethylsalicylphenyl), 2-,3- and 4-acetylphenyl, 1,8-

20   dihydroxynaphthyl (-$C_{10}H_6$-OH) and aryloxy ethyl [C_6-C_9 aryl (including phenoxy ethyl)],
2,2'-dihydroxybiphenyl, 2-, 3- and 4-N,N-dialkylaminophenol, -$C_6H_4CH_2$-N(CH_3)$_2$,

trimethoxybenzyl, triethoxybenzyl, 2-alkyl pyridinyl (C_{1-4} alkyl);
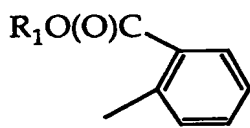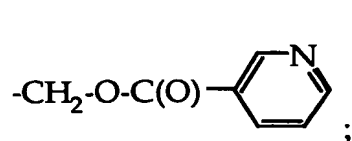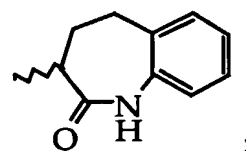
 ; C_4 - C_8 esters of 2-carboxyphenyl; and C_1-
C_4 alkylene-C_3-C_6 aryl (including benzyl, -CH_2-pyrrolyl, -CH_2-thienyl, -CH_2-imidazolyl, -

25   CH_2-oxazolyl, -CH_2-isoxazolyl, -CH_2-thiazolyl, -CH_2-isothiazolyl, -CH_2-pyrazolyl, -CH_2-
pyridinyl and -CH_2-pyrimidinyl) substituted in the aryl moiety by 3 to 5 halogen atoms or 1 to
2 atoms or groups selected from halogen, C_1-C_{12} alkoxy (including methoxy and ethoxy),
cyano, nitro, OH, C_1-C_{12} haloalkyl (1 to 6 halogen atoms; including -CH_2CCl_3), C_1-C_{12} alkyl

(including methyl and ethyl), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl; alkoxy ethyl [C_1-C_6 alkyl including -CH_2-CH_2-O-CH_3 (methoxy ethyl)]; alkyl substituted by any of the groups set forth above for aryl, in particular OH or by 1 to 3 halo atoms (including -CH_3, -$CH(CH_3)_2$, -$C(CH_3)_3$, -CH_2CH_3, -$(CH_2)_2CH_3$, -$(CH_2)_3CH_3$, -$(CH_2)_4CH_3$, -$(CH_2)_5CH_3$, -CH_2CH_2F, -

5   CH_2CH_2Cl, -CH_2CF_3, and -CH_2CCl_3); ; -N-2-propylmorpholino, 2,3-dihydro-6-hydroxyindene, sesamol, catechol monoester, -CH_2-$C(O)$-$N(R^1)_2$, -CH_2-$S(O)(R^1)$, -CH_2-$S(O)_2(R^1)$, -CH_2-$CH(OC(O)CH_2R^1)$-$CH_2(OC(O)CH_2R^1)$, cholesteryl, enolpyruvate ($HOOC$-$C(=CH_2)$-), glycerol;
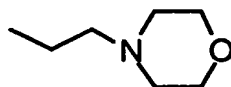
      a 5 or 6 carbon monosaccharide, disaccharide or oligosaccharide (3 to 9

10 monosaccharide residues);

      triglycerides such as α-D-β-diglycerides (wherein the fatty acids composing glyceride lipids generally are naturally occurring saturated or unsaturated C_{6-26}, C_{6-18} or C_{6-10} fatty acids such as linoleic, lauric, myristic, palmitic, stearic, oleic, palmitoleic, linolenic and the like fatty acids) linked to acyl of the parental compounds herein through a glyceryl oxygen of the

15 triglyceride;

      phospholipids linked to the carboxyl group through the phosphate of the phospholipid;

      phthalidyl (shown in Fig. 1 of Clayton et al., *Antimicrob. Agents Chemo.* (1974) 5(6):670-671;

      cyclic carbonates such as (5-R_d-2-oxo-1,3-dioxolen-4-yl) methyl esters (Sakamoto

20 et al., *Chem. Pharm. Bull.* (1984) 32(6)2241-2248) where R_d is R_1, R_4 or aryl; and
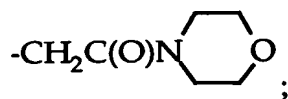
      The hydroxyl groups of the compounds of this invention optionally are substituted with one of groups III, IV or V disclosed in WO 94/21604, or with isopropyl.

25   As further embodiments, Table A lists examples of protecting group ester moieties that for example can be bonded via oxygen to -$C(O)O$- and -$P(O)(O-)_2$ groups. Several amidates also are shown, which are bound directly to -$C(O)$- or -$P(O)_2$. Esters of structures 1-5, 8-10 and 16, 17, 19-22 are synthesized by reacting the compound herein having a free hydroxyl with the corresponding halide (chloride or acyl chloride and the like) and N ,N-dicyclohexyl-N-

30 morpholine carboxamidine (or another base such as DBU, triethylamine, $CsCO_3$, N,N-

dimethylaniline and the like) in DMF (or other solvent such as acetonitrile or N-methylpyrrolidone). When the compound to be protected is a phosphonate, the esters of structures 5-7, 11, 12, 21, and 23-26 are synthesized by reaction of the alcohol or alkoxide salt (or the corresponding amines in the case of compounds such as 13, 14 and 15) with the monochlorophosphonate or dichlorophosphonate (or another activated phosphonate).

TABLE A

1. $-CH_2-C(O)-N(R_1)_2$ *
2. $-CH_2-S(O)(R_1)$
3. $-CH_2-S(O)_2(R_1)$
4. $-CH_2-O-C(O)-CH_2-C_6H_5$
5. 3-cholesteryl
6. 3-pyridyl
7. N-ethylmorpholino
8. $-CH_2-O-C(O)-C_6H_5$
9. $-CH_2-O-C(O)-CH_2CH_3$
10. $-CH_2-O-C(O)-C(CH_3)_3$
11. $-CH_2-CCl_3$
12. $-C_6H_5$
13. $-NH-CH_2-C(O)O-CH_2CH_3$
14. $-N(CH_3)-CH_2-C(O)O-CH_2CH_3$
15. $-NHR_1$
16. $-CH_2-O-C(O)-C_{10}H_{15}$
17. $-CH_2-O-C(O)-CH(CH_3)_2$
18. $-CH_2-C\#H(OC(O)CH_2R_1)-CH_2-(OC(O)CH_2R_1)$*

19. $-CH_2C(O)N$⟨morpholino⟩   20.   21.

22. $-CH_2-O-C(O)-$⟨pyridyl⟩   23. $-CH_2CH_2-$⟨pyridyl⟩   24. $CH_3O(O)C-$⟨tolyl⟩

25. $CH_3CH_2O(O)C-$⟨tolyl⟩   26. $-CH_2-$⟨3,4,5-trimethoxyphenyl⟩

- chiral center is (R), (S) or racemate.

Other esters that are suitable for use herein are described in EP 632048.

Protecting groups also includes "double ester" forming profunctionalities such as -
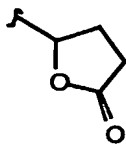
$CH_2OC(O)OCH_3$, $-CH_2SCOCH_3$, $-CH_2OCON(CH_3)_2$, or alkyl- or aryl-

acyloxyalkyl groups of the structure $-CH(R^1$ or $W^5)O((CO)R^{37})$ or

$-CH(R^1$ or $W^5)((CO)OR^{38})$ (linked to oxygen of the acidic group) wherein R^{37} and R^{38} are

alkyl, aryl, or alkylaryl groups (see U.S. patent 4,968,788). Frequently R^{37} and R^{38} are bulky

groups such as branched alkyl, ortho-substituted aryl, meta-substituted aryl, or combinations

thereof, including normal, secondary, iso- and tertiary alkyls of 1-6 carbon atoms. An example

is the pivaloyloxymethyl group. These are of particular use with prodrugs for oral

administration. Examples of such useful protecting groups are alkylacyloxymethyl esters and
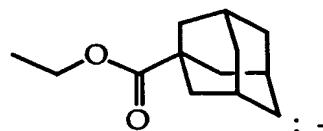
their derivatives, including $-CH(CH_2CH_2OCH_3)OC(O)C(CH_3)_3$,   ; -

$CH_2OC(O)C_{10}H_{15}$, $-CH_2OC(O)C(CH_3)_3$, $-CH(CH_2OCH_3)OC(O)C(CH_3)_3$, -

$CH(CH(CH_3)_2)OC(O)C(CH_3)_3$, $-CH_2OC(O)CH_2CH(CH_3)_2$, $-CH_2OC(O)C_6H_{11}$, -

$CH_2OC(O)C_6H_5$, $-CH_2OC(O)C_{10}H_{15}$, $-CH_2OC(O)CH_2CH_3$, $-CH_2OC(O)CH(CH_3)_2$, -

$CH_2OC(O)C(CH_3)_3$ and $-CH_2OC(O)CH_2C_6H_5$.

For prodrug purposes, the ester typically chosen is one heretofore used for antibiotic

drugs, in particular the cyclic carbonates, double esters, or the phthalidyl, aryl or alkyl esters.

In some embodiments the protected acidic group is an ester of the acidic group and is

the residue of a hydroxyl-containing functionality. In other embodiments, an amino compound

is used to protect the acid functionality. The residues of suitable hydroxyl or amino-containing

functionalities are set forth above or are found in WO 95/07920. Of particular interest are the

residues of amino acids, amino acid esters, polypeptides, or aryl alcohols. Typical amino acid,

polypeptide and carboxyl-esterified amino acid residues are described on pages 11-18 and

related text of WO 95/07920 as groups L1 or L2. WO 95/07920 expressly teaches the

amidates of phosphonic acids, but it will be understood that such amidates are formed with

any of the acid groups set forth herein and the amino acid residues set forth in WO 95/07920.

Typical esters for protecting acidic functionalities are also described in WO 95/07920,

again understanding that the same esters can be formed with the acidic groups herein as with

the phosphonate of the '920 publication. Typical ester groups are defined at least on WO 95/07920 pages 89-93 (under R^{31} or R^{35}), the table on page 105, and pages 21-23 (as R). Of particular interest are esters of unsubstituted aryl such as phenyl or arylalkyl such benzyl, or hydroxy-, halo-, alkoxy-, carboxy- and/or alkylestercarboxy-substituted aryl or alkylaryl,

5   especially phenyl, ortho-ethoxyphenyl, or C_1-C_4 alkylestercarboxyphenyl (salicylate C_1-C_{12} alkylesters).

The protected acidic groups, particularly when using the esters or amides of WO 95/07920, are useful as prodrugs for oral administration. However, it is not essential that the

10   acidic group be protected in order for the compounds of this invention to be effectively administered by the oral route. When the compounds of the invention having protected groups, in particular amino acid amidates or substituted and unsubstituted aryl esters are administered systemically or orally they are capable of hydrolytic cleavage *in vivo* to yield the free acid.

15

One or more of the acidic hydroxyls are protected. If more than one acidic hydroxyl is protected then the same or a different protecting group is employed, e.g., the esters may be different or the same, or a mixed amidate and ester may be used.

20   Typical hydroxy protecting groups described in Greene (pages 14-118) include substituted methyl and alkyl ethers, substituted benzyl ethers, silyl ethers, esters including sulfonic acid esters, and carbonates. For example:

- Ethers (methyl, *t*-butyl, allyl);
- Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, *t*-Butylthiomethyl,

25   (Phenyldimethylsilyl)methoxymethyl, Benzyloxymethyl, *p*-Methoxybenzyloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, *t*-Butoxymethyl, 4-Pentenyloxymethyl, Siloxymethyl, 2-Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyranyl, 3-Bromotetrahydropyranyl, Tetrahydropthiopyranyl, 1-Methoxycyclohexyl, 4-

30   Methoxytetrahydropyranyl, 4-Methoxytetrahydrothiopyranyl, 4-Methoxytetrahydropthiopyranyl *S,S*-Dioxido, 1-[(2-Chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-Dioxan-2-yl, Tetrahydrofuranyl, Tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl));

- Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxyethyl, 1-Methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilylethyl, 2-(Phenylselenyl)ethyl,

- *p*-Chlorophenyl, *p*-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl);

5 - Substituted Benzyl Ethers (*p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *p*-Halobenzyl, 2,6-Dichlorobenzyl, *p*-Cyanobenzyl, *p*-Phenylbenzyl, 2- and 4-Picolyl, 3-Methyl-2-picolyl *N*-Oxido, Diphenylmethyl, *p,p'*-Dinitrobenzhydryl, 5-Dibenzosuberyl, Triphenylmethyl, α-Naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, Di(*p*-methoxyphenyl)phenylmethyl, Tri(*p*-

10 methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenyldiphenylmethyl, 4,4',4''-Tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-Tris(levulinoyloxyphenyl)methyl, 4,4',4''-Tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4',4''-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzisothiazolyl *S,S*-Dioxido);

15 - Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, Dimethylisopropylsilyl, Diethylisopropylsilyl, Dimethylthexylsilyl, *t*-Butyldimethylsilyl, *t*-Butyldiphenylsilyl, Tribenzylsilyl, Tri-*p*-xylylsilyl, Triphenylsilyl, Diphenylmethylsilyl, *t*-Butylmethoxyphenylsilyl);

- Esters (Formate, Benzoylformate, Acetate, Choroacetate, Dichloroacetate,
20 Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, *p*-Chlorophenoxyacetate, *p*-poly-Phenylacetate, 3-Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, *p*-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate));

25 - Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, *p*-Nitrophenyl, Benzyl, *p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *S*-Benzyl Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate);

30 - Groups With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Nitro-4-methylpentanoate, *o*-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl Carbonate, 4-(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate); Miscellaneous Esters (2,6-Dichloro-4-

methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3 tetramethylbutyl)phenoxyacetate, 2,4-
Bis(1,1-dimethylpropyl)phenoxyacetate, Chlorodiphenylacetate, Isobutyrate,
Monosuccinate, (E)-2-Methyl-2-butenoate (Tigloate), o-(Methoxycarbonyl)benzoate, p-
poly-Benzoate, α-Naphthoate, Nitrate, Alkyl N,N,N',N'-Tetramethylphosphorodiamidate,
N-Phenylcarbamate, Borate, Dimethylphosphinothioyl, 2,4-Dinitrophenylsulfenate); and

- Sulfonates (Sulfate, Methanesulfonate (Mesylate), Benzylsulfonate, Tosylate).

- Typical 1,2-diol protecting groups (thus, generally where two OH groups are taken
  together with the protecting functionality) are described in Greene at pages 118-142 and
  include Cyclic Acetals and Ketals (Methylene, Ethylidene, 1-t-Butylethylidene, 1-
  Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-Trichloroethylidene, Acetonide
  (Isopropylidene), Cyclopentylidene, Cyclohexylidene, Cycloheptylidene, Benzylidene, p-
  Methoxybenzylidene, 2,4-Dimethoxybenzylidene, 3,4-Dimethoxybenzylidene, 2-
  Nitrobenzylidene); Cyclic Ortho Esters (Methoxymethylene, Ethoxymethylene,
  Dimethoxymethylene, 1-Methoxyethylidene, 1-Ethoxyethylidine, 1,2-
  Dimethoxyethylidene, α-Methoxybenzylidene, 1-(N,N-Dimethylamino)ethylidene
  Derivative, α -(N,N-Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); Silyl
  Derivatives (Di-t-butylsilylene Group, 1,3-(1,1,3,3-Tetraisopropyldisiloxanylidene), and
  Tetra-t-butoxydisiloxane-1,3-diylidene), Cyclic Carbonates, Cyclic Boronates, Ethyl
  Boronate and Phenyl Boronate.

More typically, 1,2-diol protecting groups include those shown in Table B, still more
typically, epoxides, acetonides, cyclic ketals and aryl acetals.

Table B
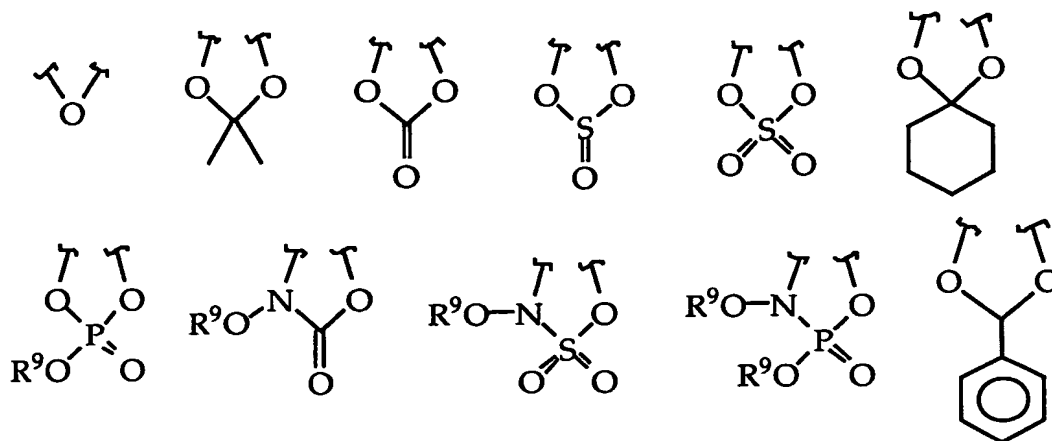
wherein R^9 is C$_1$-C$_6$ alkyl.

Amino protecting groups

Another set of protecting groups include any of the typical amino protecting groups described by Greene at pages 315-385. They include:

- Carbamates: (methyl and ethyl, 9-fluorenylmethyl, 9(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 4-methoxyphenacyl);

- Substituted Ethyl: (2,2,2-trichoroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'- and 4'-pyridyl)ethyl, 2-(*N*,*N*-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl);

- Groups With Assisted Cleavage: (2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-choro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl);

- Groups Capable of Photolytic Cleavage: (*m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl(*o*-nitrophenyl)methyl); Urea-Type Derivatives (phenothiazinyl-(10)-carbonyl, *N'*-*p*-toluenesulfonylaminocarbonyl, *N'*-

phenylaminothiocarbonyl);

- Miscellaneous Carbamates: (*t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N*,*N*-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(*N*,*N*-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, *p*-(*p*'-Methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-trimethylbenzyl);

- Amides: (*N*-formyl, *N*-acetyl, *N*-choroacetyl, *N*-trichoroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridylcarboxamide, *N*-benzoylphenylalanyl, *N*-benzoyl, *N*-*p*-phenylbenzoyl);

- Amides With Assisted Cleavage: (*N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N*'-dithiobenzyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxyphenyl)propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, 4,5-diphenyl-3-oxazolin-2-one);

- Cyclic Imide Derivatives: (*N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenylmaleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3-5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridonyl);

- *N*-Alkyl and *N*-Aryl Amines: (*N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, *N*-2-picolylamine *N*'-oxide);

- Imine Derivatives: (*N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*,(*N*',*N*'-dimethylaminomethylene, *N*,*N*'-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, *N*-cyclohexylidene);

- Enamine Derivatives: (*N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl));

- *N*-Metal Derivatives (*N*-borane derivatives, *N*-diphenylborinic acid derivatives, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, *N*-copper or *N*-zinc chelate);

- N-N Derivatives: (*N*-nitro, *N*-nitroso, *N*-oxide);

- N-P Derivatives: (*N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, *N*-diphenyl phosphoryl);

- N-Si Derivatives, N-S Derivatives, and N-Sulfenyl Derivatives: (*N*-benzenesulfenyl, *N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl, *N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxybenzenesulfenyl, *N*-triphenylmethylsulfenyl, *N*-3-nitropyridinesulfenyl); and *N*-sulfonyl Derivatives (*N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxybenzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6,-tetramethyl-4-methoxybenzenesulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy-4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*-β-trimethylsilyethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, *N*-phenacylsulfonyl).

More typically, protected amino groups include carbamates and amides, still more typically, $-NHC(O)R^1$ or $-N=CR^1N(R^1)_2$. Another protecting group, also useful as a prodrug for amino or $-NH(R^5)$, is:
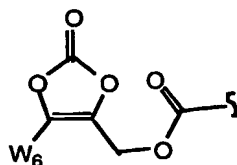
See for example Alexander, J. etal (1996) *J. Med. Chem.* 39:480-486.

Amino acid and polypeptide protecting group and conjugates

An amino acid or polypeptide protecting group of a compound of the invention has the structure $R^{15}NHCH(R^{16})C(O)$-, where R^{15} is H, an amino acid or polypeptide residue, or R^5, and R^{16} is defined below.

R^{16} is lower alkyl or lower alkyl (C_1-C_6) substituted with amino, carboxyl, amide, carboxyl ester, hydroxyl, C_6-C_7 aryl, guanidinyl, imidazolyl, indolyl, sulfhydryl, sulfoxide, and/or alkylphosphate. R^{10} also is taken together with the amino acid α N to form a proline

residue (R^{10} = -CH$_2$)$_3$-). However, R^{10} is generally the side group of a naturally-occurring amino acid such as H, -CH$_3$, -CH(CH$_3$)$_2$, -CH$_2$-CH(CH$_3$)$_2$, -CHCH$_3$-CH$_2$-CH$_3$, -CH$_2$-C$_6$H$_5$, -CH$_2$CH$_2$-S-CH$_3$, -CH$_2$OH, -CH(OH)-CH$_3$, -CH$_2$-SH, -CH$_2$-C$_6$H$_4$OH, -CH$_2$-CO-NH$_2$, -CH$_2$-CH$_2$-CO-NH$_2$, -CH$_2$-COOH, -CH$_2$-CH$_2$-COOH, -(CH$_2$)$_4$-NH$_2$ and -(CH$_2$)$_3$-NH-

5   C(NH$_2$)-NH$_2$. R$_{10}$ also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl.

Another set of protecting groups include the residue of an amino-containing compound, in particular an amino acid, a polypeptide, a protecting group, -NHSO$_2$R,

10   NHC(O)R, -N(R)$_2$, NH$_2$ or -NH(R)(H), whereby for example a carboxylic acid is reacted, i.e. coupled, with the amine to form an amide, as in C(O)NR$_2$. A phosphonic acid may be reacted with the amine to form a phosphonamidate, as in -P(O)(OR)(NR$_2$).

In general, amino acids have the structure R^{17}C(O)CH(R^{16})NH-, where R^{17} is -OH, -

15   OR, an amino acid or a polypeptide residue. Amino acids are low molecular weight compounds, on the order of less than about 1000 MW and which contain at least one amino or imino group and at least one carboxyl group. Generally the amino acids will be found in nature, i.e., can be detected in biological material such as bacteria or other microbes, plants, animals or man. Suitable amino acids typically are alpha amino acids, i.e. compounds

20   characterized by one amino or imino nitrogen atom separated from the carbon atom of one carboxyl group by a single substituted or unsubstituted alpha carbon atom. Of particular interest are hydrophobic residues such as mono-or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues contribute to cell permeability by increasing the partition coefficient of the parental drug. Typically, the residue does not

25   contain a sulfhydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof. Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids

30   are glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline. Additionally, unnatural amino acids, for example, valanine, phenylglycine and homoarginine are also included. Commonly

encountered amino acids that are not gene-encoded may also be used in the present invention. All of the amino acids used in the present invention may be either the D- or L- optical isomer. In addition, other peptidomimetics are also useful in the present invention. For a general review, see Spatola, A. F., in *Chemistry and Biochemistry of Amino Acids, Peptides and*

5   *Proteins*, B. Weinstein, eds., Marcel Dekker, New York, p. 267 (1983).

       When protecting groups are single amino acid residues or polypeptides they optionally are substituted at R^3 of substituents A^1, A^2 or A^3, or substituted at R_3 of substituents A_1, A_2 or A_3. These conjugates are produced by forming an amide bond between a carboxyl group of

10   the amino acid (or C-terminal amino acid of a polypeptide for example). Similarly, conjugates are formed between R^3 or R_3 and an amino group of an amino acid or polypeptide. Generally, only one of any site in the parental molecule is amidated with an amino acid as described herein, although it is within the scope of this invention to introduce amino acids at more than one permitted site. Usually, a carboxyl group of R^3 is amidated with an amino acid. In

15   general, the α-amino or α-carboxyl group of the amino acid or the terminal amino or carboxyl group of a polypeptide are bonded to the parental functionalities, i.e., carboxyl or amino groups in the amino acid side chains generally are not used to form the amide bonds with the parental compound (although these groups may need to be protected during synthesis of the conjugates as described further below).

20

       With respect to the carboxyl-containing side chains of amino acids or polypeptides it will be understood that the carboxyl group optionally will be blocked, e.g. by R^1, esterified with R^5 or amidated. Similarly, the amino side chains R^{16} optionally will be blocked with R^1 or substituted with R^5.

25

       Such ester or amide bonds with side chain amino or carboxyl groups, like the esters or amides with the parental molecule, optionally are hydrolyzable *in vivo* or *in vitro* under acidic (pH <3) or basic (pH >10) conditions. Alternatively, they are substantially stable in the gastrointestinal tract of humans but are hydrolyzed enzymatically in blood or in intracellular

30   environments. The esters or amino acid or polypeptide amidates also are useful as intermediates for the preparation of the parental molecule containing free amino or carboxyl groups. The free acid or base of the parental compound, for example, is readily formed from the esters or amino acid or polypeptide conjugates of this invention by conventional hydrolysis procedures.

When an amino acid residue contains one or more chiral centers, any of the D, L, meso, threo or erythro (as appropriate) racemates, scalemates or mixtures thereof may be used. In general, if the intermediates are to be hydrolyzed non-enzymatically (as would be the case where the amides are used as chemical intermediates for the free acids or free amines), D

5   isomers are useful. On the other hand,the linkerisomers are more versatile since they can be susceptible to both non-enzymatic and enzymatic hydrolysis, and are more efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acids whose residues are represented by R^x or R^y include

10   the following:

Glycine;

Aminopolycarboxylic acids, e.g., aspartic acid, β-hydroxyaspartic acid, glutamic acid, β -hydroxyglutamic acid, β-methylaspartic acid, β-methylglutamic acid, β, β-dimethylaspartic acid, γ-hydroxyglutamic acid, β, γ-dihydroxyglutamic acid, β -phenylglutamic acid, γ-

15   methyleneglutamic acid, 3-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid;

Amino acid amides such as glutamine and asparagine;

Polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β -aminoalanine, γ -aminobutyrine, ornithine, citruline, homoarginine, homocitrulline,

20   hydroxylysine, allohydroxylsine and diaminobutyric acid;

Other basic amino acid residues such as histidine;

Diaminodicarboxylic acids such as α, α'-diaminosuccinic acid, α, α'-diaminoglutaric acid, α, α'-diaminoadipic acid, α, α'-diaminopimelic acid, α, α'-diamino- β-hydroxypimelic acid, α, α'-diaminosuberic acid, α, α'-diaminoazelaic acid, and α, α'-diaminosebacic acid;

25   Imino acids such as proline, hydroxyproline, allohydroxyproline, γ-methylproline, pipecolic acid, 5-hydroxypipecolic acid, and azetidine-2-carboxylic acid;

A mono- or di-alkyl (typically C_1-C_8 branched or normal) amino acid such as alanine, valine, leucine, allylglycine, butyrine, norvaline, norleucine, heptyline, α-methylserine, α-amino-α-methyl-γ-hydroxyvaleric acid, α-amino- α-methyl-δ-hydroxyvaleric acid, α-amino- α-

30   methyl-ε-hydroxycaproic acid, isovaline, α-methylglutamic acid, α-aminoisobutyric acid, α-aminodiethylacetic acid, α-aminodiisopropylacetic acid, α-aminodi-n-propylacetic acid, α-aminodiisobutylacetic acid, α-aminodi-n-butylacetic acid, α-aminoethylisopropylacetic acid, α-amino-n-propylacetic acid, α-aminodiisoamyacetic acid, α-methylaspartic acid, α-methylglutamic acid, 1-aminocyclopropane-1-carboxylic acid, isoleucine, alloisoleucine, *tert-*

leucine, β-methyltryptophan and α-amino- β-ethyl-β-phenylpropionic acid;

β-phenylserinyl;

Aliphatic α-amino-β-hydroxy acids such as serine, β-hydroxyleucine, β-hydroxynorleucine, β -hydroxynorvaline, and α-amino-β-hydroxystearic acid;

α-Amino, α-, γ-, δ- or ε-hydroxy acids such as homoserine, δ -hydroxynorvaline, γ-hydroxynorvaline and ε-hydroxynorleucine residues; canavine and canaline; γ -hydroxyornithine;

2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid;

α-Amino-β-thiols such as penicillamine, β-thiolnorvaline or β-thiolbutyrine;

Other sulfur containing amino acid residues including cysteine; homocystine, β-phenylmethionine, methionine, S-allyl-L-cysteine sulfoxide, 2-thiolhistidine, cystathionine, and thiol ethers of cysteine or homocysteine;

Phenylalanine, tryptophan and ring-substituted α-amino acids such as the phenyl- or cyclohexylamino acids α-aminophenylacetic acid, α-aminocyclohexylacetic acid and α-amino-β-cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl, lower alkyl, hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (e.g., tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dichloro, *o*-, *m*- or *p*-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitro-phenylalanine); furyl-, thienyl-, pyridyl-, pyrimidinyl-, purinyl- or naphthyl-alanines; and tryptophan analogues and derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan;

α-Amino substituted amino acids including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-benzylvaline; and

α-Hydroxy and substituted α -hydroxy amino acids including serine, threonine, allothreonine, phosphoserine and phosphothreonine.

Polypeptides are polymers of amino acids in which a carboxyl group of one amino acid monomer is bonded to an amino or imino group of the next amino acid monomer by an amide bond. Polypeptides include dipeptides, low molecular weight polypeptides (about 1500-5000 MW) and proteins. Proteins optionally contain 3, 5, 10, 50, 75, 100 or more residues, and suitably are substantially sequence-homologous with human, animal, plant or microbial proteins. They include enzymes (e.g., hydrogen peroxidase) as well as immunogens such as KLH, or antibodies or proteins of any type against which one wishes to raise an immune response. The nature and identity of the polypeptide may vary widely.

The polypeptide amidates are useful as immunogens in raising antibodies against either

the polypeptide (if it is not immunogenic in the animal to which it is administered) or against the epitopes on the remainder of the compound of this invention.

Antibodies capable of binding to the parental non-peptidyl compound are used to separate the parental compound from mixtures, for example in diagnosis or manufacturing of the parental compound. The conjugates of parental compound and polypeptide generally are more immunogenic than the polypeptides in closely homologous animals, and therefore make the polypeptide more immunogenic for facilitating raising antibodies against it. Accordingly, the polypeptide or protein may not need to be immunogenic in an animal typically used to raise antibodies, e.g., rabbit, mouse, horse, or rat, but the final product conjugate should be immunogenic in at least one of such animals. The polypeptide optionally contains a peptidolytic enzyme cleavage site at the peptide bond between the first and second residues adjacent to the acidic heteroatom. Such cleavage sites are flanked by enzymatic recognition structures, e.g. a particular sequence of residues recognized by a peptidolytic enzyme.

Peptidolytic enzymes for cleaving the polypeptide conjugates of this invention are well known, and in particular include carboxypeptidases. Carboxypeptidases digest polypeptides by removing C-terminal residues, and are specific in many instances for particular C-terminal sequences. Such enzymes and their substrate requirements in general are well known. For example, a dipeptide (having a given pair of residues and a free carboxyl terminus) is covalently bonded through its α-amino group to the phosphorus or carbon atoms of the compounds herein. In embodiments where W_1 is phosphonate it is expected that this peptide will be cleaved by the appropriate peptidolytic enzyme, leaving the carboxyl of the proximal amino acid residue to autocatalytically cleave the phosphonoamidate bond.

Suitable dipeptidyl groups (designated by their single letter code) are AA, AR, AN, AD, AC, AE, AQ, AG, AH, AI, AL, AK, AM, AF, AP, AS, AT, AW, AY, AV, RA, RR, RN, RD, RC, RE, RQ, RG, RH, RI, RL, RK, RM, RF, RP, RS, RT, RW, RY, RV, NA, NR, NN, ND, NC, NE, NQ, NG, NH, NI, NL, NK, NM, NF, NP, NS, NT, NW, NY, NV, DA, DR, DN, DD, DC, DE, DQ, DG, DH, DI, DL, DK, DM, DF, DP, DS, DT, DW, DY, DV, CA, CR, CN, CD, CC, CE, CQ, CG, CH, CI, CL, CK, CM, CF, CP, CS, CT, CW, CY, CV, EA, ER, EN, ED, EC, EE, EQ, EG, EH, EI, EL, EK, EM, EF, EP, ES, ET, EW, EY, EV, QA, QR, QN, QD, QC, QE, QQ, QG, QH, QI, QL, QK, QM, QF, QP, QS, QT, QW, QY, QV, GA, GR, GN, GD, GC, GE, GQ, GG, GH, GI, GL, GK, GM, GF, GP, GS, GT, GW, GY,

GV, HA, HR, HN, HD, HC, HE, HQ, HG, HH, HI, HL, HK, HM, HF, HP, HS, HT, HW,

HY, HV, IA, IR, IN, ID, IC, IE, IQ, IG, IH, II, IL, IK, IM, IF, IP, IS, IT, IW, IY, IV, LA,

LR, LN, LD, LC, LE, LQ, LG, LH, LI, LL, LK, LM, LF, LP, LS, LT, LW, LY, LV, KA, KR,

KN, KD, KC, KE, KQ, KG, KH, KI, KL, KK, KM, KF, KP, KS, KT, KW, KY, KV, MA,

MR, MN, MD, MC, ME, MQ, MG, MH, MI, ML, MK, MM, MF, MP, MS, MT, MW, MY,

MV, FA, FR, FN, FD, FC, FE, FQ, FG, FH, FI, FL, FK, FM, FF, FP, FS, FT, FW, FY, FV,

PA, PR, PN, PD, PC, PE, PQ, PG, PH, PI, PL, PK, PM, PF, PP, PS, PT, PW, PY, PV, SA,

SR, SN, SD, SC, SE, SQ, SG, SH, SI, SL, SK, SM, SF, SP, SS, ST, SW, SY, SV, TA, TR,

TN, TD, TC, TE, TQ, TG, TH, TI, TL, TK, TM, TF, TP, TS, TT, TW, TY, TV, WA, WR,

WN, WD, WC, WE, WQ, WG, WH, WI, WL, WK, WM, WF, WP, WS, WT, WW, WY,

WV, YA, YR, YN, YD, YC, YE, YQ, YG, YH, YI, YL, YK, YM, YF, YP, YS, YT, YW,

YY, YV, VA, VR, VN, VD, VC, VE, VQ, VG, VH, VI, VL, VK, VM, VF, VP, VS, VT,

VW, VY and VV.

Tripeptide residues are also useful as protecting groups. When a phosphonate is to be protected, the sequence $-X^4-pro-X^5-$ (where X^4 is any amino acid residue and X^5 is an amino acid residue, a carboxyl ester of proline, or hydrogen) will be cleaved by luminal carboxypeptidase to yield X^4 with a free carboxyl, which in turn is expected to autocatalytically cleave the phosphonoamidate bond. The carboxy group of X^5 optionally is esterified with benzyl.

Dipeptide or tripeptide species can be selected on the basis of known transport properties and/or susceptibility to peptidases that can affect transport to intestinal mucosal or other cell types. Dipeptides and tripeptides lacking an α-amino group are transport substrates for the peptide transporter found in brush border membrane of intestinal mucosal cells (Bai, J.P.F., (1992) *Pharm Res.* 9:969-978. Transport competent peptides can thus be used to enhance bioavailability of the amidate compounds. Di- or tripeptides having one or more amino acids in the D configuration are also compatible with peptide transport and can be utilized in the amidate compounds of this invention. Amino acids in the D configuration can be used to reduce the susceptibility of a di- or tripeptide to hydrolysis by proteases common to the brush border such as aminopeptidase N. In addition, di- or tripeptides alternatively are selected on the basis of their relative resistance to hydrolysis by proteases found in the lumen of the intestine. For example, tripeptides or polypeptides lacking asp and/or glu are poor substrates for aminopeptidase A, di- or tripeptides lacking amino acid residues on the N-

terminal side of hydrophobic amino acids (leu, tyr, phe, val, trp) are poor substrates for

endopeptidase, and peptides lacking a pro residue at the penultimate position at a free

carboxyl terminus are poor substrates for carboxypeptidase P. Similar considerations can also

be applied to the selection of peptides that are either relatively resistant or relatively

5   susceptible to hydrolysis by cytosolic, renal, hepatic, serum or other peptidases. Such poorly

cleaved polypeptide amidates are immunogens or are useful for bonding to proteins in order to

prepare immunogens.

Prototype compounds contain at least one functional group capable of bonding to the

10   phosphorus atom in the phosphonate moiety. The phosphonate candidate compounds are

cleaved intracellularly after they have reached the desired site of action, e.g., inside a lymphoid

cell. The mechanism by which this occurs is further described below in the examples. As

noted, the free acid of the phosphonate is phosphorylated in the cell..

15   From the foregoing, it will be apparent that many different prototypes can be

derivatized in accord with the present invention. Numerous such prototypes are specifically

mentioned herein. However, it should be understood that the discussion of anti-HIVdrug

families and their specific members for derivatization according to this invention is not

intended to be exhaustive, but merely illustrative.

20

When the prototype compound contains multiple reactive hydroxyl functions, a

mixture of intermediates and final products may be obtained. In the unusual case in which all

hydroxy groups are approximately equally reactive, there is not expected to be a single,

predominant product, as each mono-substituted product will be obtained in approximately

25   equal amounts, while a lesser amount of multiple-substituted candidate compound will also

result. Generally speaking, however, one of the hydroxyl groups will be more susceptible to

substitution than the other(s), e.g. a primary hydroxyl will be more reactive than a secondary

hydroxyl, an unhindered hydroxyl will be more reactive than a hindered one. Consequently,

the major product will be a mono-substituted one in which the most reactive hydroxyl has

30   been derivatized while other mono-substituted and multiply-substituted products may be

obtained as minor products.

Stereoisomers

The candidate compounds may have chiral centers, e.g. chiral carbon or phosphorus

atoms. The compounds thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures.

5   Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all suitable for use as candidate compounds. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases

10   followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

      The compounds can also exist as tautomeric isomers in certain cases. All though only

15   one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

20   The optimal absolute configuration at the phosphorus atom for use in candidate compounds is that of GS-7340, depicted in the examples.

Salts and Hydrates

      Any reference to any of the compounds of the invention also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the

25   compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1–C_4 alkyl). Physiologically acceptable salts of a hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic

30   acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids.

Physiologically acceptable salts of a compound of an hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a C_1–C_4 alkyl group).

5   For therapeutic use, salts of active ingredients of the candidate compounds will be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived form a physiologically acceptable acid or base,

10   are within the scope of the present invention.

Pharmaceutically acceptable non-toxic salts of candidate compounds containing, for example, Na^+, Li^+, K^+, Ca^{+2} and Mg^{+2}, fall within the scope herein. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal

15   ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. Monovalent salts are preferred if a water soluble salt is desired.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+,

20   Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic acids, e.g., HCl, HBr, H_2SO_4, H_3PO_4 or organic sulfonic acids, to basic centers, typically

25   amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Salts of the candidate compounds with amino acids also fall within the scope of this

30   invention. Any of the amino acids described above are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Methods for Assay of Anti-HIV Activity

The anti-HIV activity of a candidate compound is assayed by any method heretofore known for determining inhibition of growth, replication, or other characteristic of HIV infection, including direct and indirect methods of detecting HIV activity. Quantitative,

5   qualitative, and semiquantitative methods of determining HIV activity are all contemplated. Typically any one of the *in vitro* or cell culture screening methods known to the art are employed, as are clinical trials in humans, studies in animal models (SIV), and the like. In screening candidate compounds it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay is often the primary

10   screening tool. Candidate compounds having an *in vitro* Ki (inhibitory constant) of less then about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for *in vivo* development, but the analytical point of selection of a candidate compound for further development is essentially a matter of choice.

Pharmaceutical Formulations

15   Candidate compounds selected for further development *in vivo* are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set

20   forth in the "Handbook of Pharmaceutical Excipients" (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

25   While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible

30   with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The

formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier

5   which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

       Formulations of candidate compounds suitable for oral administration may be

10   presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

15   A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient

20   moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

       For infections of the eye or other external tissues e.g. mouth and skin, the formulations

25   are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base.

30   Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

       If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as

propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl

5   sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier

10   with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

15   Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired

20   cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as

25   Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise a

30   combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil

suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may
5   be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a
10   dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

15   The pharmaceutical compositions of the candidate compounds may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and
20   hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

25

The pharmaceutical compositions of the candidate compounds may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile
30   injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any

bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the

active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of HIV infections as described below.

5

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

10   Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

15

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared

20   from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above

25   the formulations of candidate compounds may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active

30   ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary

compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention are used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention

5   ("controlled release formulations") in which the release of the active ingredient are controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given active ingredient.

An effective dose of candidate compound depends at least on the nature of the

10   condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active HIV infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from

15   about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

20   Routes of Administration
One or more candidate compounds (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like.

25   It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy
Candidate compound are also used in combination with other active ingredients. Such

30   combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco- compounds. Other active ingredients include adefovir dipivoxil and/or any other product currently marketed for therapy of HIV infection.properties. It is also possible to

combine any compound of the invention with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to an HIV infected patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more

5   administrations. Second and third active ingredients in the combination may have anti-HIV activity and include HIV.

The combination therapy may be synergistic, i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the

10   compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g. in separate tablets, pills or

15   capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together. A synergistic anti-viral effect denotes an antiviral effect which is greater than the predicted purely additive effects of the individual compounds of the combination.

20   <u>Metabolites of the Candidate Compounds</u>

The candidate compounds are metabolized *in vivo*. In particular, the group R^x is hydrolytically cleaved to produce a charged metabolite, and in some cases the substituents on the phosphonate such as $-Y^2[P((=Y^1)(Y^2))_{m2}R^x]_2$ are hydrolyzed as well. An example showing exemplary metabolites is found in the examples herein. While this example is concerned with

25   the metabolites of GS-7340, a nucleotide analogue, the metabolic changes to be found with candidate compounds are believed to be substantially the same at the phosphonate substituent. This charged metabolite functions as an intracellular depot form of the candidate. However, other changes may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic

30   processes. Accordingly, candidate compounds include metabolites of candidate compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g. C^{14} or H^3) compound of the invention,

administering it parenterally in a detectable dose (e.g. greater than about 0.5 mg/kg) to an

animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for

metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion

products from the urine, blood or other biological samples. These products are easily isolated

5   since they are labeled (others are isolated by the use of antibodies capable of binding epitopes

surviving in the metabolite). The metabolite structures are determined in conventional fashion,

e.g. by MS or NMR analysis. In general, analysis of metabolites is done in the same way as

conventional drug metabolism studies well-known to those skilled in the art. The conversion

products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for

10   therapeutic dosing of the candidate compounds even if they possess no HIV inhibitory activity

of their own.

Recipes and methods for determining stability of compounds in surrogate

gastrointestinal secretions are known. Compounds are defined herein as stable in the

15   gastrointestinal tract where less than about 50 mole percent of the protected groups are

deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37 °C.

Simply because the compounds are stable to the gastrointestinal tract does not mean that they

cannot be hydrolyzed *in vivo*. The phosphonate prodrugs of the invention typically will be

stable in the digestive system but are substantially hydrolyzed to the parental drug in the

20   digestive lumen, liver or other metabolic organ, or within cells in general.

Exemplary Methods of Making Candidate Compounds.

The candidate compounds are prepared by any of the applicable techniques of organic

synthesis. Many such techniques are well known in the art. However, many of the known

techniques are elaborated in "Compendium of Organic Synthetic Methods" (John Wiley &

25   Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison

and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy

G. Wade, jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as

March, J., "Advanced Organic Chemistry, Third Edition", (John Wiley & Sons, New York,

1985), "Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern

30   Organic Chemistry. In 9 Volumes", Barry M. Trost, Editor-in-Chief (Pergamon Press, New

York, 1993 printing).

Dialkyl phosphonates may be prepared according to the methods of: Quast etal (1974)

Synthesis 490; Stowell etal (1990) *Tetrahedron Lett.* 3261; US Patent No. 5663159.

        In general, synthesis of phosphonate esters is achieved by coupling a nucleophile amine
or alcohol with the corresponding activated phosphonate electrophilic precursor. For
5   example, chlorophosphonate addition on to 5'-hydroxy of nucleoside is a well known method
for preparation of nucleoside phosphate monoesters. The activated precursor can be prepared
by several well known methods. Chlorophosphonates useful for synthesis of the prodrugs are
prepared from the substituted-1,3-propanediol (Wissner, etal, (1992) *J. Med Chem.* 35:1650).
Chlorophosphonates are made by oxidation of the corresponding chlorophospholanes
10   (Anderson, etal, (1984) *J. Org. Chem.* 49:1304) which are obtained by reaction of the
substituted diol with phosphorus trichloride. Alternatively, the chlorophosphonate agent is
made by treating substituted-1,3-diols with phosphorusoxychloride (Patois, etal, (1990) *J.
Chem. Soc. Perkin Trans. I*, 1577). Chlorophosphonate species may also be generated in situ
from corresponding cyclic phosphites (Silverburg, etal., (1996) *Tetrahedron lett.*, 37:771-
15   774), which in turn can be either made from chlorophospholane or phosphoramidate
intermediate. The phosphoroflouridate intermediate prepared either from pyrophosphate or
phosphoric acid may also act as precursor in preparation of cyclic prodrugs (Watanabe etal.,
(1988) *Tetrahedron lett.*, 29:5763-66).

        Candidate compounds comprising a prodrug functionality may also be prepared from
20   the free acid by Mitsunobu reactions (Mitsunobu, (1981) *Synthesis*, 1; Campbell, (1992) *J.
Org. Chem.*, 52:6331), and other acid coupling reagents including, but not limited to,
carbodiimides (Alexander, etal, (1994) *Collect. Czech. Chem. Commun.* 59:1853; Casara, etal,
(1992) *Bioorg. Med. Chem. Lett.*, 2:145; Ohashi, etal, (1988) *Tetrahedron Lett.*, 29:1189),
and benzotriazolyloxytris-(dimethylamino)phosphonium salts (Campagne, etal, (1993)
25   *Tetrahedron Lett.*, 34:6743).

        Aryl halides undergo Ni^{+2} catalyzed reaction with phosphite derivatives to give aryl
phosphonate containing compounds (Balthazar, etal (1980) *J. Org. Chem.* 45:5425).
Phosphonates may also be prepared from the chlorophosphonate in the presence of a
30   palladium catalyst using aromatic triflates (Petrakis, etal, (1987) *J. Am. Chem. Soc.*109:2831;
Lu, etal, (1987) *Synthesis*, 726). In another method, aryl phosphonate esters are prepared
from aryl phosphates under anionic rearrangement conditions (Melvin (1981) *Tetrahedron
Lett.* 22:3375; Casteel, etal, (1991) *Synthesis*, 691). N-Alkoxy aryl salts with alkali metal
derivatives of cyclic alkyl phosphonate provide general synthesis for heteroaryl-2-phosphonate

linkers (Redmore (1970) *J. Org. Chem.* 35:4114). These above mentioned methods can also be extended to compounds where the W^5 group is a heterocycle. Cyclic-1,3-propanyl prodrugs of phosphonates are also synthesized from phosphonic diacids and substituted propane-1,3-diols using a coupling reagent such as 1,3-dicyclohexylcarbodiimide (DCC) in presence of a base (e.g., pyridine). Other carbodiimide based coupling agents like 1,3-disopropylcarbodiimide or water soluble reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) can also be utilized for the synthesis of cyclic phosphonate prodrugs.

The carbamoyl group may be formed by reaction of a hydroxy group according to the methods known in the art, including the teachings of Ellis, U.S. 2002/0103378 A1 and Hajima, U.S. 6,018,049.

A number of exemplary methods for the preparation of the candidate compounds are provided below. These methods are intended to illustrate the nature of such preparations and do not limit the scope of this invention. Many of the compounds set forth below have been screened and demonstrated to have anti-HIV activity. In view of this these compounds are no longer candidate compounds for use in the screening method of this invention. However, they are illustrative of the manner in which the artisan can substitute prototype compouns with A^3 in various ways. In addition, taken cumulatively, they are illustrative of the typical component candidate compounds to be found in a screening library.

Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20 °C), although for metal hydride reductions frequently the temperature is reduced to 0 °C to -100 °C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room

temperature, although for non-equilibrating, kinetically controlled condensations reduced

temperatures (0 °C to -100 °C) are also common. Solvents can be either protic (common in

5   equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and

use of anhydrous reaction conditions (e.g. inert gas environments) are common in the art and

will be applied when applicable.

10   Schemes

General aspects of these exemplary methods are described below and in the Examples.

Each of the products of the following processeses are optionally separated, isolated, and/or

purified prior to its use in subsequent processes.

15   The terms "treated", "treating", "treatment", and the like, mean contacting, mixing,

reacting, allowing to react, bringing into contact, and other terms common in the art for

indicating that one or more chemical entities is treated in such a manner as to convert it to one

or more other chemical entities. This means that "treating compound one with compound

two" is synonymous with "allowing compound one to react with compound two", "contacting

20   compound one with compound two", "reacting compound one with compound two", and

other expressions common in the art of organic synthesis for reasonably indicating that

compound one was "treated", "reacted", "allowed to react", etc., with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are

25   allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M),

temperatures (-100 °C to 250 °C, typically -78 °C to 150 °C, more typically -78 °C to 100 °C,

still more typically 0 °C to 100 °C), reaction vessels (typically glass, plastic, metal), solvents,

pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or

argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The

30   knowledge of similar reactions known in the art of organic synthesis are used in selecting the

conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill

in the art of organic synthesis selects conditions and apparatus reasonably expected to

successfully carry out the chemical reactions of the described processes based on the

knowledge in the art.

Modifications of each of the exemplary schemes above and in the examples (hereafter "exemplary schemes") leads to various analogs of the candidate compounds. The above cited

5 citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of

10 homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale

15 analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting

20 material, reaction by product, or the like. Such reagents include adsorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

25

Selection of appropriate methods of separation depends on the nature of the materials involved. These include boiling point and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply

30 techniques most likely to achieve the desired separation.

A single stereoisomer, e.g. an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents ("Stereochemistry of Carbon

Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113:(3) 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2)

5   formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

Under method (1), diastereomeric salts can be formed by reaction of enantiomerically

10   pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic

15   acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994)

20   Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g. (-)

25   menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of

30   atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers

can be distinguished by methods used to distinguish other chiral molecules with asymmetric
carbon atoms, such as optical rotation and circular dichroism.

The articles "and" and "or" shall be construed as meaning "and/or" unless otherwise
required by context or useage. Use of "and/or" herein shall not be construed as foreclosing
5   "and/or" when only "and" or "or" are employed in other circumstances.

This invention includes all novel and unobvious compounds disclosed herein, whether
or not such compounds are described in the context of methods or other disclosure and
whether or not such compounds are claimed upon filing or are set forth in the summary of
10   invention.

The invention has been described in detail sufficient to allow one of ordinary skill in the
art to make and use the subject matter of the following examples. It is apparent that certain
modifications of the methods and compositions of the following examples can be made within
15   the scope and spirit of the invention.

Examples General Section

Some Examples have been performed multiple times. In repeated Examples, reaction
conditions such as time, temperature, concentration and the like, and yields were within
normal experimental ranges. In repeated Examples where significant modifications were
20   made, these have been noted where the results varied significantly from those described. In
Examples where different starting materials were used, these are noted. When the repeated
Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl
ester", this intends that an otherwise present group, in this case typically a methyl ester, is
taken to be the same group modified as indicated.

25

Exemplary Methods of Making the Compounds of the Invention.

The invention provides many methods of making the compositions of the invention.
The compositions are prepared by any of the applicable techniques of organic synthesis. Many
such techniques are well known in the art. Such as those elaborated in "Compendium of
30   Organic Synthetic Methods" (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and
Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S.
Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, jr., 1980; Vol. 5, Leroy G. Wade,
Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., "Advanced Organic Chemistry,

Third Edition", (John Wiley & Sons, New York, 1985), "Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes", Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

5   Dialkyl phosphonates may be prepared according to the methods of: Quast et al (1974) *Synthesis* 490; Stowell et al (1990) *Tetrahedron Lett.* 3261; US Patent No. 5663159.

In general, synthesis of phosphonate esters is achieved by coupling a nucleophile amine or alcohol with the corresponding activated phosphonate electrophilic precursor for example, Chlorophosphonate addition on to 5'-hydroxy of nucleoside is a well known method for preparation of nucleoside phosphate monoesters. The activated precursor can be prepared by

10   several well known methods. Chlorophosphonates useful for synthesis of the prodrugs are prepared from the substituted-1,3-propanediol (Wissner, et al, (1992) *J. Med Chem.* 35:1650). Chlorophosphonates are made by oxidation of the corresponding chlorophospholanes (Anderson, et al, (1984) *J. Org. Chem.* 49:1304) which are obtained by reaction of the substituted diol with phosphorus trichloride. Alternatively, the chlorophosphonate agent is

15   made by treating substituted-1,3-diols with phosphorusoxychloride (Patois, et al, (1990) *J. Chem. Soc. Perkin Trans. I*, 1577). Chlorophosphonate species may also be generated in situ from corresponding cyclic phosphites (Silverburg, et al., (1996) *Tetrahedron lett.*, 37:771-774), which in turn can be either made from chlorophospholane or phosphoramidate intermediate. Phosphoroflouridate intermediate prepared either from pyrophosphate or

20   phosphoric acid may also act as precursor in preparation of cyclic prodrugs (Watanabe et al., (1988) *Tetrahedron lett.*, 29:5763-66). <u>Caution</u>: fluorophosphonate compounds may be highly toxic!

<u>Schemes and Examples</u>

General aspects of these exemplary methods are described below and in the Examples.

25   Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

A number of exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods.

30   The terms "treated", "treating", "treatment", and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound

two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two.

5   "Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or

10   argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the

15   knowledge in the art.

Modifications of each of the exemplary schemes above and in the examples (hereafter "exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

20   In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation,

25   sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

30   Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material,

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binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation,

5   presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.
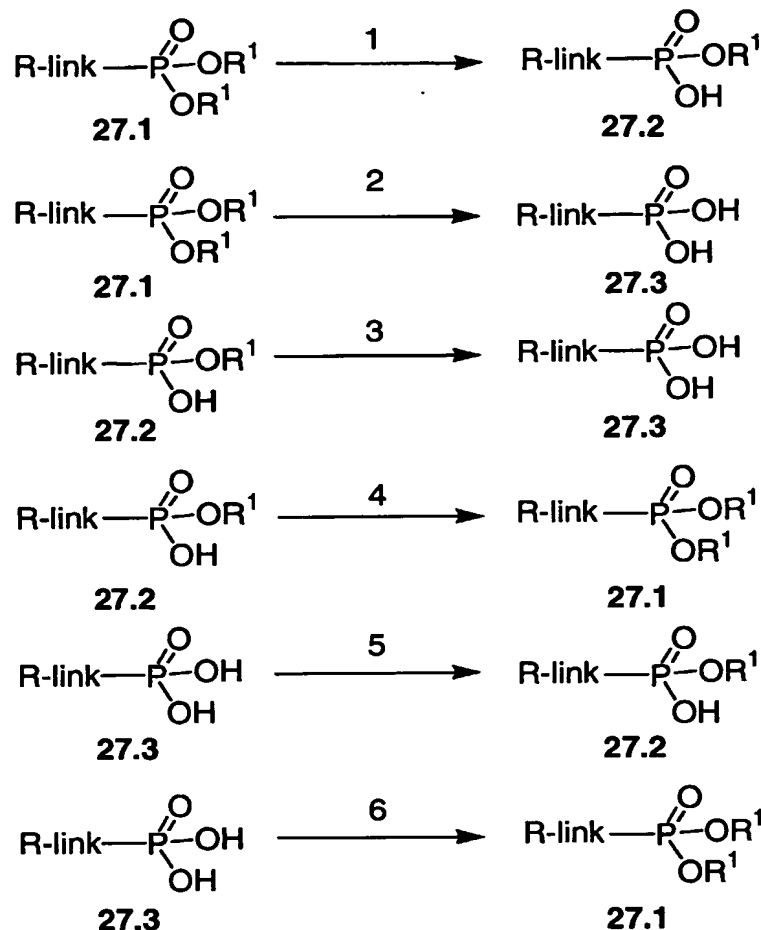
A single stereoisomer, e.g. an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of

10   diastereomers using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113:(3) 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2)

15   formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine

20   (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric

25   salts.

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure

30   chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g. (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-

(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic

mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric

diastereomers. Stable diastereomers of atropisomeric compounds can be separated and

isolated by normal- and reverse-phase chromatography following methods for separation of

5   atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic

mixture of two enantiomers can be separated by chromatography using a chiral stationary

phase ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed. Chapman and Hall, New

York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers

can be distinguished by methods used to distinguish other chiral molecules with asymmetric

10   carbon atoms, such as optical rotation and circular dichroism.

All literature and patent citations above are hereby expressly incorporated by reference

at the locations of their citation. Specifically cited sections or pages of the above cited works

are incorporated by reference with specificity. The invention has been described in detail

sufficient to allow one of ordinary skill in the art to make and use the subject matter of the

15   following Embodiments. It is apparent that certain modifications of the methods and

compositions of the following Embodiments can be made within the scope and spirit of the

invention.

Scheme A

R-link —P(=O)(OR^1)—OR^1 →[1] R-link —P(=O)(OR^1)—OH
27.1   **27.2**

R-link —P(=O)(OR^1)—OR^1 →[2] R-link—P(=O)(OH)—OH
27.1   **27.3**

R-link —P(=O)(OR^1)—OH →[3] R-link—P(=O)(OH)—OH
27.2   **27.3**

R-link —P(=O)(OR^1)—OH →[4] R-link —P(=O)(OR^1)—OR^1
27.2   **27.1**

R-link—P(=O)(OH)—OH →[5] R-link —P(=O)(OR^1)—OH
27.3   **27.2**

R-link—P(=O)(OH)—OH →[6] R-link —P(=O)(OR^1)—OR^1
27.3   **27.1**

Scheme A shows the general interconversions of certain phosphonate compounds:

5   acids -P(O)(OH)$_2$; mono-esters -P(O)(OR$_1$)(OH); and diesters -P(O)(OR$_1$)$_2$ in which the R^1

groups are independently selected, and defined herein before, and the phosphorus is attached

through a carbon moiety (link, i.e. linker), which is attached to the rest of the molecule, e.g.

drug or drug intermediate (R). The R^1 groups attached to the phosphonate esters in Scheme 1

may be changed using established chemical transformations. The interconversions may be

10   carried out in the precursor compounds or the final products using the methods described

below. The methods employed for a given phosphonate transformation depend on the nature

of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in

Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **27.1** into the corresponding phosphonate

15   monoester **27.2** (Scheme A, Reaction 1) can be accomplished by a number of methods. For

example, the ester **27.1** in which R^1 is an arylalkyl group such as benzyl, can be converted into

the monoester compound **27.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in *J. Org. Chem.*, 1995, 60:2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester **27.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **27.2** can be effected by treatment of the ester **27.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **27.2** in which one of the groups R^1 is arylalkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **27.2** in which R^1 is alkyl, by hydrogenation, for example using a palladium on carbon catalyst.

Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, can be converted into the monoester **27.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in *J. Org. Chem.*, 38:3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **27.1** or a phosphonate monoester **27.2** into the corresponding phosphonic acid **27.3** (Scheme A, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in *J. Chem. Soc., Chem. Comm.*, 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **27.2** in which R^1 is arylalkyl such as benzyl, can be converted into the corresponding phosphonic acid **27.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxane. A phosphonate monoester **27.2** in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **27.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68:618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **27.1** in which R^1 is benzyl is described in *J. Org. Chem.*, 24:434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **27.1** in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, 78:2336, 1956.

The conversion of a phosphonate monoester **27.2** into a phosphonate diester **27.1** (Scheme A, Reaction 4) in which the newly introduced R^1 group is alkyl, arylalkyl, or haloalkyl such as chloroethyl, can be effected by a number of reactions in which the substrate

27.2 is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-

5   yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **27.1**

10   to the diester **27.1** can be effected by the use of the Mitsunobu reaction. The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **27.2** can be transformed into the phosphonate diester **27.1**, in which the introduced R^1 group is alkenyl or arylalkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as

15   alkenyl or arylalkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **27.2** is transformed into the chloro analog $-P(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like,

20   as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $-P(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **27.1**.

       A phosphonic acid $-P(O)(OH)_2$ can be transformed into a phosphonate monoester $-$

25     $P(O)(OR^1)(OH)$ (Scheme A, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $-P(O)(OR^1)_2$ **27.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

       A phosphonic acid $-P(O)(OH)_2$ **27.3** can be transformed into a phosphonate diester $-$ $P(O)(OR^1)_2$ **27.1** (Scheme A, Reaction 6) by a coupling reaction with the hydroxy compound

30   R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **27.3** can be transformed into phosphonic esters **27.1** in which R^1 is aryl, such as phenyl, by means of a coupling reaction employing, for example, phenol and dicyclohexylcarbodiimide in pyridine at about 70°C. Alternatively, phosphonic acids **27.3** can

be transformed into phosphonic esters **27.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^{1}Br in a polar organic solvent such as acetonitrile solution at reflux temperature, in the presence of a base such as cesium carbonate, to afford the phosphonic ester **27.1**.

5   Phosphonate prodrugs of the present invention may also be prepared from the precursor free acid by Mitsunobu reactions (Mitsunobu, (1981) *Synthesis*, 1; Campbell, (1992) *J. Org. Chem.*, 52:6331), and other acid coupling reagents including, but not limited to, carbodiimides (Alexander, et al, (1994) *Collect. Czech. Chem. Commun.* 59:1853; Casara, et al, (1992) *Bioorg. Med. Chem. Lett.*, 2:145; Ohashi, et al, (1988) *Tetrahedron Lett.*, 29:1189),

10   and benzotriazolyloxytris-(dimethylamino)phosphonium salts (Campagne, et al, (1993) *Tetrahedron Lett.*, 34:6743).

Preparation of carboalkoxy-substituted phosphonate bisamidates, monoamidates, diesters and monoesters.

15

A number of methods are available for the conversion of phosphonic acids into amidates and esters. In one group of methods, the phosphonic acid is either converted into an isolated activated intermediate such as a phosphoryl chloride, or the phosphonic acid is activated in situ for reaction with an amine or a hydroxy compound.

20

The conversion of phosphonic acids into phosphoryl chlorides is accomplished by reaction with thionyl chloride, for example as described in J. Gen. Chem. USSR, 1983, 53, 480, Zh. Obschei Khim., 1958, 28, 1063, or J. Org. Chem., 1994, 59, 6144, or by reaction with oxalyl chloride, as described in J. Am. Chem. Soc., 1994, 116, 3251, or J. Org. Chem., 1994, 59,

25   6144, or by reaction with phosphorus pentachloride, as described in J. Org. Chem., 2001, 66, 329, or in J. Med. Chem., 1995, 38, 1372. The resultant phosphoryl chlorides are then reacted with amines or hydroxy compounds in the presence of a base to afford the amidate or ester products.

30   Phosphonic acids are converted into activated imidazolyl derivatives by reaction with carbonyl diimidazole, as described in J. Chem. Soc., Chem. Comm., 1991, 312, or Nucleosides Nucleotides 2000, 19, 1885. Activated sulfonyloxy derivatives are obtained by the reaction of phosphonic acids with trichloromethylsulfonyl chloride, as described in J. Med. Chem. 1995, 38, 4958, or with triisopropylbenzenesulfonyl chloride, as described in Tet. Lett., 1996, 7857,

or Bioorg. Med. Chem. Lett., 1998, 8, 663. The activated sulfonyloxy derivatives are then reacted with amines or hydroxy compounds to afford amidates or esters.

Alternatively, the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a diimide coupling agent. The preparation of phosphonic amidates and esters by means of coupling reactions in the presence of dicyclohexyl carbodiimide is described, for example, in J. Chem. Soc., Chem. Comm., 1991, 312, or J. Med. Chem., 1980, 23, 1299 or Coll. Czech. Chem. Comm., 1987, 52, 2792. The use of ethyl dimethylaminopropyl carbodiimide for activation and coupling of phosphonic acids is described in Tet. Lett., 2001, 42, 8841, or Nucleosides Nucleotides, 2000, 19, 1885.

A number of additional coupling reagents have been described for the preparation of amidates and esters from phosphonic acids. The agents include Aldrithiol-2, and PYBOP and BOP, as described in J. Org. Chem., 1995, 60, 5214, and J. Med. Chem., 1997, 40, 3842, mesitylene-2-sulfonyl-3-nitro-1,2,4-triazole (MSNT), as described in J. Med. Chem., 1996, 39, 4958, diphenylphosphoryl azide, as described in J. Org. Chem., 1984, 49, 1158, 1-(2,4,6-triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole (TPSNT) as described in Bioorg. Med. Chem. Lett., 1998, 8, 1013, bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP), as described in Tet. Lett., 1996, 37, 3997, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphinane, as described in Nucleosides Nucleotides 1995, 14, 871, and diphenyl chlorophosphate, as described in J. Med. Chem., 1988, 31, 1305.

Phosphonic acids are converted into amidates and esters by means of the Mitsonobu reaction, in which the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The procedure is described in Org. Lett., 2001, 3, 643, or J. Med. Chem., 1997, 40, 3842.

Phosphonic esters are also obtained by the reaction between phosphonic acids and halo compounds, in the presence of a suitable base. The method is described, for example, in Anal. Chem., 1987, 59, 1056, or J. Chem. Soc. Perkin Trans., I, 1993, 19, 2303, or J. Med. Chem., 1995, 38, 1372, or Tet. Lett., 2002, 43, 1161.

Schemes 1 - 4 illustrate the conversion of phosphonate esters and phosphonic acids into carboalkoxy-substituted phosphorobisamidates (Scheme 1), phosphoroamidates (Scheme 2), phosphonate monoesters (Scheme 3) and phosphonate diesters, (Scheme 4).

Scheme 1 illustrates various methods for the conversion of phosphonate diesters **1.1** into

phosphorobisamidates **1.5**. The diester **1.1**, prepared as described previously, is hydrolyzed,

either to the monoester **1.2** or to the phosphonic acid **1.6**. The methods employed for these

5   transformations are described above. The monoester **1.2** is converted into the monoamidate

1.3 by reaction with an aminoester **1.9**, in which the group R^2 is H or alkyl, the group R^4 is an

alkylene moiety such as, for example, $CHCH_3$, $CHPr^j$, $CH(CH_2Ph)$, $CH_2CH(CH_3)$ and the like,

or a group present in natural or modified aminoacids, and the group R^5 is alkyl. The reactants

are combined in the presence of a coupling agent such as a carbodiimide, for example

10   dicyclohexyl carbodiimide, as described in J. Am. Chem. Soc., 1957, 79, 3575, optionally in

the presence of an activating agent such as hydroxybenztriazole, to yield the amidate product

1.3. The amidate-forming reaction is also effected in the presence of coupling agents such as

BOP, as described in J. Org. Chem., 1995, 60, 5214, Aldrithiol, PYBOP and similar coupling

agents used for the preparation of amides and esters. Alternatively, the reactants **1.2** and **1.9**

15   are transformed into the monoamidate **1.3** by means of a Mitsonobu reaction. The preparation

of amidates by means of the Mitsonobu reaction is described in J. Med. Chem., 1995, 38,

2742. Equimolar amounts of the reactants are combined in an inert solvent such as

tetrahydrofuran in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The

thus-obtained monoamidate ester **1.3** is then transformed into amidate phosphonic acid **1.4**.

20   The conditions used for the hydrolysis reaction depend on the nature of the R^1 group, as

described previously. The phosphonic acid amidate **1.4** is then reacted with an aminoester **1.9**,

as described above, to yield the bisamidate product **1.5**, in which the amino substituents are

the same or different.

25   An example of this procedure is shown in Scheme 1, Example 1. In this procedure, a dibenzyl

phosphonate **1.14** is reacted with diazabicyclooctane (DABCO) in toluene at reflux, as

described in J. Org. Chem., 1995, 60, 2946, to afford the monobenzyl phosphonate **1.15**. The

product is then reacted with equimolar amounts of ethyl alaninate **1.16** and dicyclohexyl

carbodiimide in pyridine, to yield the amidate product **1.17**. The benzyl group is then

30   removed, for example by hydrogenolysis over a palladium catalyst, to give the monoacid

product **1.18**. This compound is then reacted in a Mitsonobu reaction with ethyl leucinate

1.19, triphenyl phosphine and diethylazodicarboxylate, as described in J. Med. Chem., 1995,

38, 2742, to produce the bisamidate product **1.20**.

Using the above procedures, but employing, in place of ethyl leucinate **1.19** or ethyl alaninate **1.16**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

5   Alternatively, the phosphonic acid **1.6** is converted into the bisamidate **1.5** by use of the coupling reactions described above. The reaction is performed in one step, in which case the nitrogen-related substituents present in the product **1.5** are the same, or in two steps, in which case the nitrogen-related substituents can be different.

An example of the method is shown in Scheme 1, Example 2. In this procedure, a phosphonic
10   acid **1.6** is reacted in pyridine solution with excess ethyl phenylalaninate **1.21** and dicyclohexylcarbodiimide, for example as described in J. Chem. Soc., Chem. Comm., 1991, 1063, to give the bisamidate product **1.22**.

Using the above procedures, but employing, in place of ethyl phenylalaninate, different
15   aminoesters **1.9**, the corresponding products **1.5** are obtained.

As a further alternative, the phosphonic acid **1.6** is converted into the mono or bis-activated derivative **1.7**, in which Lv is a leaving group such as chloro, imidazolyl, triisopropylbenzenesulfonyloxy etc. The conversion of phosphonic acids into chlorides **1.7**
20   (Lv = Cl) is effected by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17. The conversion of phosphonic acids into monoimidazolides **1.7** (Lv = imidazolyl) is described in J. Med. Chem., 2002, 45, 1284 and in J. Chem. Soc. Chem. Comm., 1991, 312. Alternatively, the phosphonic acid is activated by reaction with triisopropylbenzenesulfonyl
25   chloride, as described in Nucleosides and Nucleotides, 2000, 10, 1885. The activated product is then reacted with the aminoester **1.9**, in the presence of a base, to give the bisamidate **1.5**. The reaction is performed in one step, in which case the nitrogen substituents present in the product **1.5** are the same, or in two steps, via the intermediate **1.11**, in which case the nitrogen substituents can be different.

30

Examples of these methods are shown in Scheme 1, Examples 3 and 5. In the procedure illustrated in Scheme 1, Example 3, a phosphonic acid **1.6** is reacted with ten molar equivalents of thionyl chloride, as described in Zh. Obschei Khim., 1958, 28, 1063, to give the

dichloro compound **1.23**. The product is then reacted at reflux temperature in a polar aprotic solvent such as acetonitrile, and in the presence of a base such as triethylamine, with butyl serinate **1.24** to afford the bisamidate product **1.25**.

5   Using the above procedures, but employing, in place of butyl serinate **1.24**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

In the procedure illustrated in Scheme 1, Example 5, the phosphonic acid **1.6** is reacted, as described in J. Chem. Soc. Chem. Comm., 1991, 312, with carbonyl diimidazole to give the

10   imidazolide **1.32**. The product is then reacted in acetonitrile solution at ambient temperature, with one molar equivalent of ethyl alaninate **1.33** to yield the monodisplacement product **1.34**. The latter compound is then reacted with carbonyl diimidazole to produce the activated intermediate **1.35**, and the product is then reacted, under the same conditions, with ethyl N-methylalaninate **1.33a** to give the bisamidate product **1.36**.

15

Using the above procedures, but employing, in place of ethyl alaninate **1.33** or ethyl N-methylalaninate **1.33a**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

The intermediate monoamidate **1.3** is also prepared from the monoester **1.2** by first converting

20   the monoester into the activated derivative **1.8** in which Lv is a leaving group such as halo, imidazolyl etc, using the procedures described above. The product **1.8** is then reacted with an aminoester **1.9** in the presence of a base such as pyridine, to give an intermediate monoamidate product **1.3**. The latter compound is then converted, by removal of the R^1 group and coupling of the product with the aminoester **1.9**, as described above, into the bisamidate **1.5**.

25

An example of this procedure, in which the phosphonic acid is activated by conversion to the chloro derivative **1.26**, is shown in Scheme 1, Example 4. In this procedure, the phosphonic monobenzyl ester **1.15** is reacted, in dichloromethane, with thionyl chloride, as described in Tet. Let., 1994, 35, 4097, to afford the phosphoryl chloride **1.26**. The product is then reacted

30   in acetonitrile solution at ambient temperature with one molar equivalent of ethyl 3-amino-2-methylpropionate **1.27** to yield the monoamidate product **1.28**. The latter compound is hydrogenated in ethyl acetate over a 5% palladium on carbon catalyst to produce the monoacid product **1.29**. The product is subjected to a Mitsonobu coupling procedure, with

equimolar amounts of butyl alaninate **1.30**, triphenyl phosphine, diethylazodicarboxylate and triethylamine in tetrahydrofuran, to give the bisamidate product **1.31**.

Using the above procedures, but employing, in place of ethyl 3-amino-2-methylpropionate

5   **1.27** or butyl alaninate **1.30**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

The activated phosphonic acid derivative **1.7** is also converted into the bisamidate **1.5** via the diamino compound **1.10**. The conversion of activated phosphonic acid derivatives such as

10   phosphoryl chlorides into the corresponding amino analogs **1.10**, by reaction with ammonia, is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976. The diamino compound **1.10** is then reacted at elevated temperature with a haloester **1.12**, in a polar organic solvent such as dimethylformamide, in the presence of a base such as dimethylaminopyridine or potassium carbonate, to yield the bisamidate **1.5**.

15   An example of this procedure is shown in Scheme **1**, Example **6**. In this method, a dichlorophosphonate **1.23** is reacted with ammonia to afford the diamide **1.37**. The reaction is performed in aqueous, aqueous alcoholic or alcoholic solution, at reflux temperature. The resulting diamino compound is then reacted with two molar equivalents of ethyl 2-bromo-3-methylbutyrate **1.38**, in a polar organic solvent such as N-methylpyrrolidinone at ca. 150°C, in

20   the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the bisamidate product **1.39**.

Using the above procedures, but employing, in place of ethyl 2-bromo-3-methylbutyrate **1.38**, different haloesters **1.12** the corresponding products **1.5** are obtained.

25

The procedures shown in Scheme **1** are also applicable to the preparation of bisamidates in which the aminoester moiety incorporates different functional groups. Scheme **1**, Example **7** illustrates the preparation of bisamidates derived from tyrosine. In this procedure, the monoimidazolide **1.32** is reacted with propyl tyrosinate **1.40**, as described in Example **5**, to

30   yield the monoamidate **1.41**. The product is reacted with carbonyl diimidazole to give the imidazolide **1.42**, and this material is reacted with a further molar equivalent of propyl tyrosinate to produce the bisamidate product **1.43**.

Using the above procedures, but employing, in place of propyl tyrosinate **1.40**, different

aminoesters **1.9**, the corresponding products **1.5** are obtained. The aminoesters employed in

the two stages of the above procedure can be the same or different, so that bisamidates with

the same or different amino substituents are prepared.

5

Scheme 2 illustrates methods for the preparation of phosphonate monoamidates.

In one procedure, a phosphonate monoester **1.1** is converted, as described in Scheme 1, into

the activated derivative **1.8**. This compound is then reacted, as described above, with an

aminoester **1.9**, in the presence of a base, to afford the monoamidate product **2.1**.

10   The procedure is illustrated in Scheme 2, Example 1. In this method, a monophenyl

phosphonate **2.7** is reacted with, for example, thionyl chloride, as described in J. Gen. Chem.

USSR., 1983, 32, 367, to give the chloro product **2.8**. The product is then reacted, as

described in Scheme 1, with ethyl alaninate **2.9**, to yield the amidate **2.10**.

15   Using the above procedures, but employing, in place of ethyl alaninate **2.9**, different

aminoesters **1.9**, the corresponding products **2.1** are obtained.

Alternatively, the phosphonate monoester **1.1** is coupled, as described in Scheme 1, with an

aminoester **1.9** to produce the amidate **2.1**. If necessary, the R^1 substituent is then altered, by

20   initial cleavage to afford the phosphonic acid **2.2**. The procedures for this transformation

depend on the nature of the R^1 group, and are described above. The phosphonic acid is then

transformed into the ester amidate product **2.3**, by reaction with the hydroxy compound

R^3OH, in which the group R^3 is aryl, heteroaryl, alkyl, cycloalkyl, haloalkyl etc, using the same

coupling procedures (carbodiimide, Aldrithiol-2, PYBOP, Mitsonobu reaction etc) described

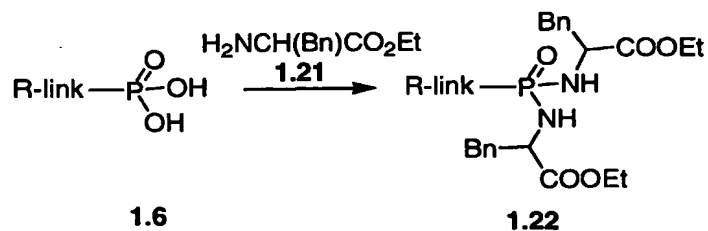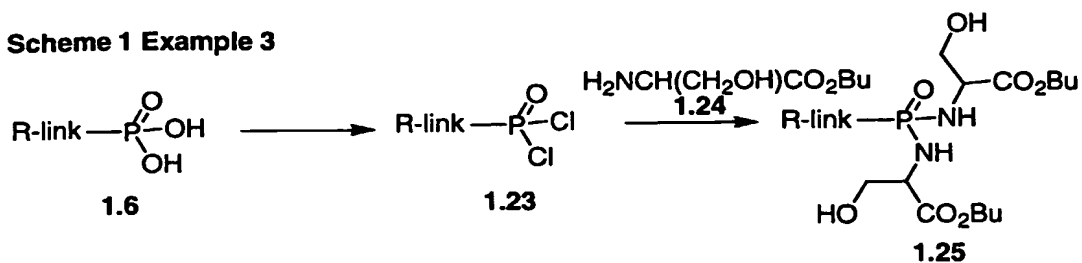25   in Scheme 1 for the coupling of amines and phosphonic acids.
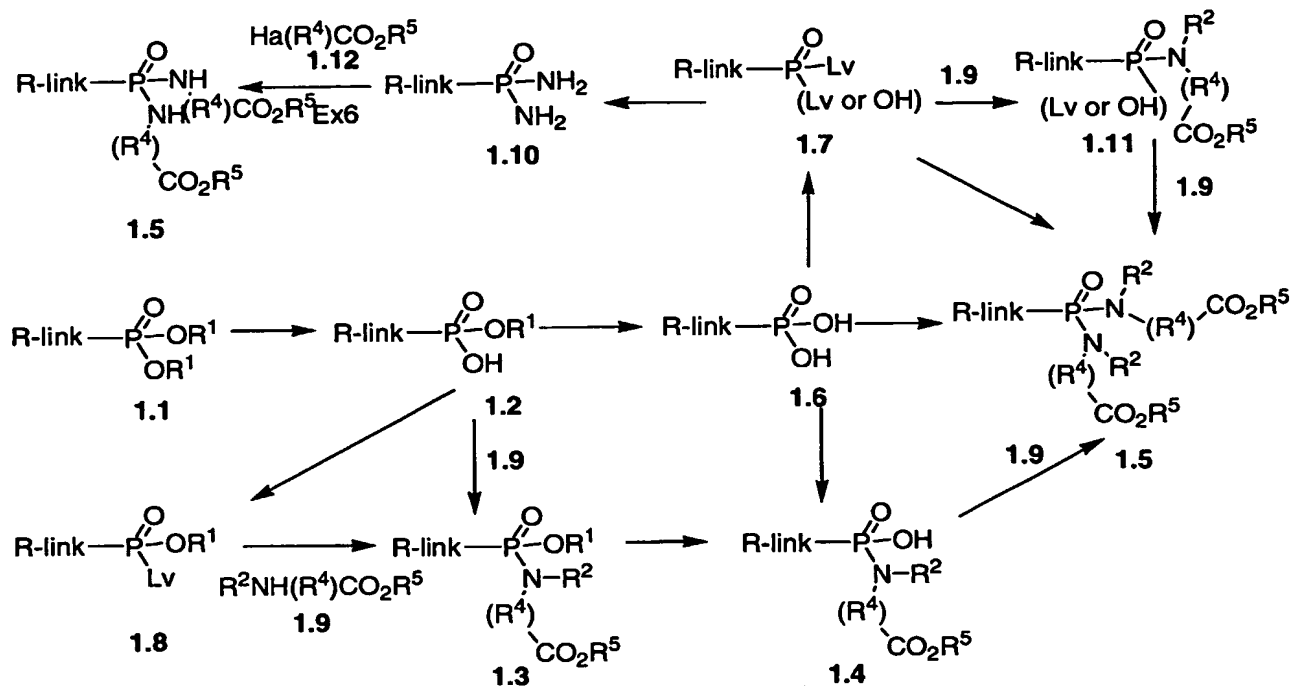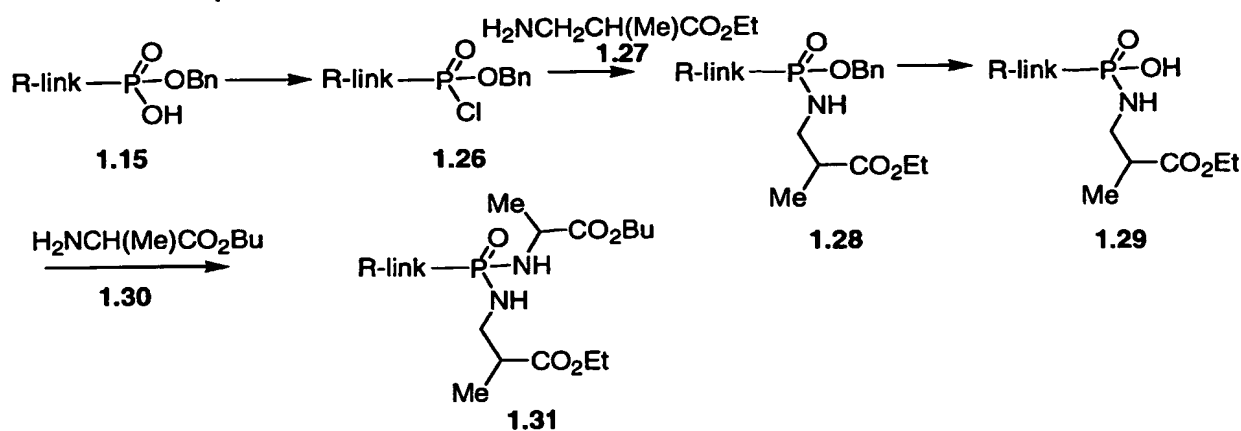
Scheme 1

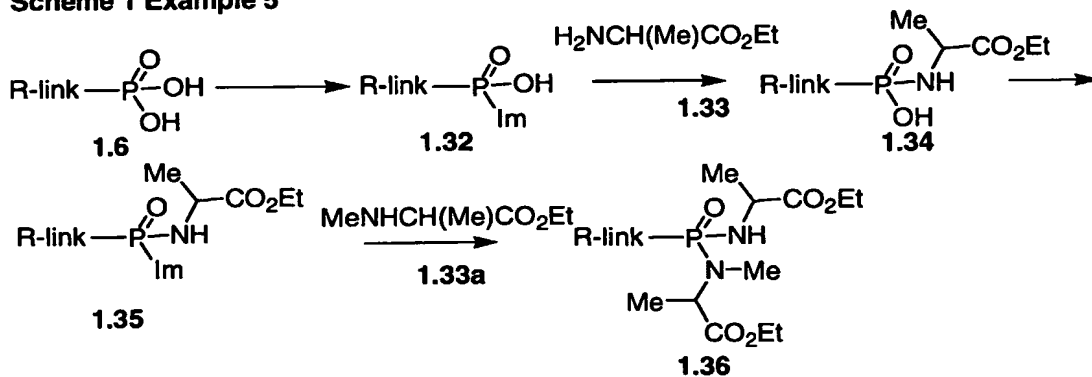
Scheme 1 Example 1
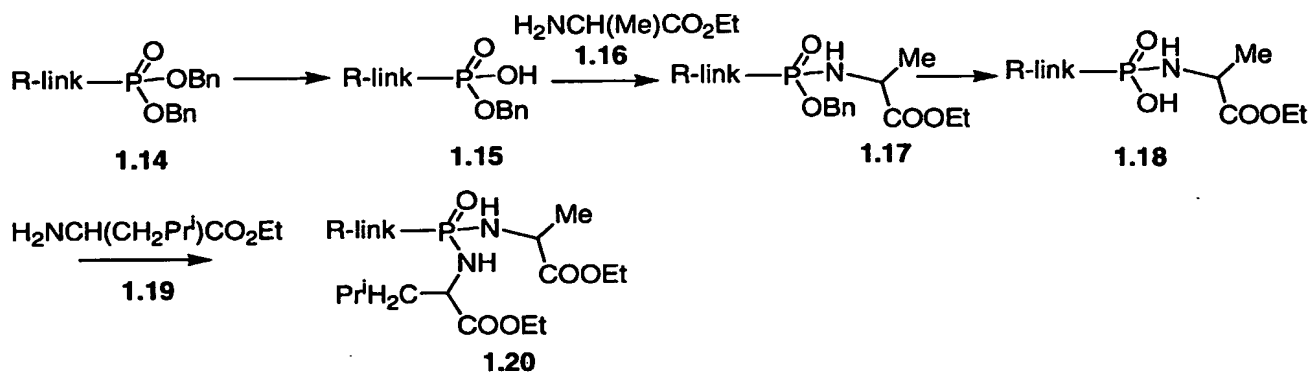
Scheme 1 Example 2

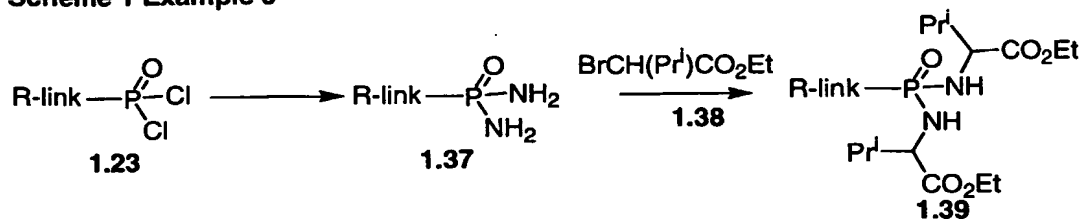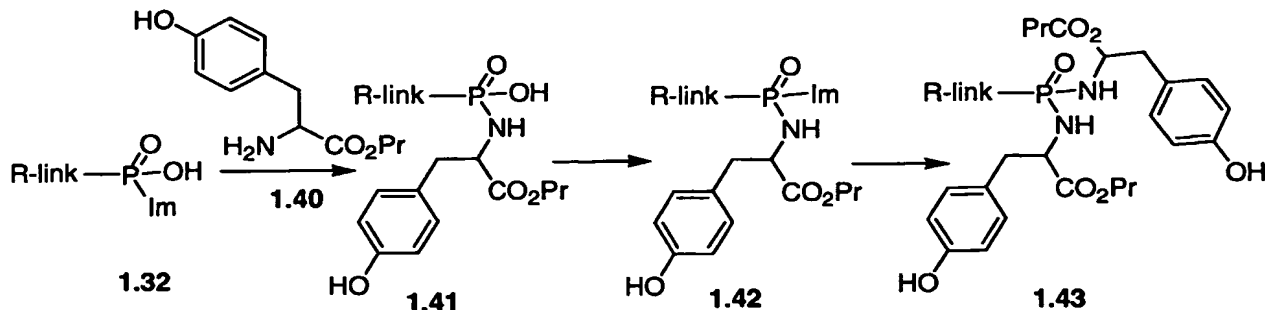**Scheme 1 Example 3**

Scheme 1 Example 4

Scheme 1 Example 5

Scheme 1 Example 6

Scheme 1 Example 7

Examples of this method are shown in Scheme 2, Examples and 2 and 3. In the sequence

shown in Example 2, a monobenzyl phosphonate **2.11** is transformed by reaction with ethyl

5   alaninate, using one of the methods described above, into the monoamidate **2.12**. The benzyl

group is then removed by catalytic hydrogenation in ethyl acetate solution over a 5%

palladium on carbon catalyst, to afford the phosphonic acid amidate **2.13**. The product is then

reacted in dichloromethane solution at ambient temperature with equimolar amounts of 1-

(dimethylaminopropyl)-3-ethylcarbodiimide and trifluoroethanol **2.14**, for example as

10   described in Tet. Lett., 2001, 42, 8841, to yield the amidate ester **2.15**.

In the sequence shown in Scheme 2, Example 3, the monoamidate **2.13** is coupled, in

tetrahydrofuran solution at ambient temperature, with equimolar amounts of dicyclohexyl

carbodiimide and 4-hydroxy-N-methylpiperidine **2.16**, to produce the amidate ester product

15   **2.17**.

Using the above procedures, but employing, in place of the ethyl alaninate product **2.12**

different monoacids **2.2**, and in place of trifluoroethanol **2.14** or 4-hydroxy-N-methylpiperidine

2.16, different hydroxy compounds R³OH, the corresponding products **2.3** are obtained.

20

Alternatively, the activated phosphonate ester **1.8** is reacted with ammonia to yield the amidate

2.4. The product is then reacted, as described in Scheme 1, with a haloester **2.5**, in the

presence of a base, to produce the amidate product **2.6**. If appropriate, the nature of the R¹

group is changed, using the procedures described above, to give the product **2.3**. The method

25   is illustrated in Scheme 2, Example 4. In this sequence, the monophenyl phosphoryl chloride

2.18 is reacted, as described in Scheme 1, with ammonia, to yield the amino product **2.19**.

This material is then reacted in N-methylpyrrolidinone solution at 170°C with butyl 2-bromo-3-phenylpropionate **2.20** and potassium carbonate, to afford the amidate product **2.21**.

Using these procedures, but employing, in place of butyl 2-bromo-3-phenylpropionate **2.20**, different haloesters **2.5**, the corresponding products **2.6** are obtained.

5

The monoamidate products **2.3** are also prepared from the doubly activated phosphonate derivatives **1.7**. In this procedure, examples of which are described in Synlett., 1998, 1, 73, the intermediate **1.7** is reacted with a limited amount of the aminoester **1.9** to give the mono-displacement product **1.11**. The latter compound is then reacted with the hydroxy compound

10 R^{3}OH in a polar organic solvent such as dimethylformamide, in the presence of a base such as diisopropylethylamine, to yield the monoamidate ester **2.3**.
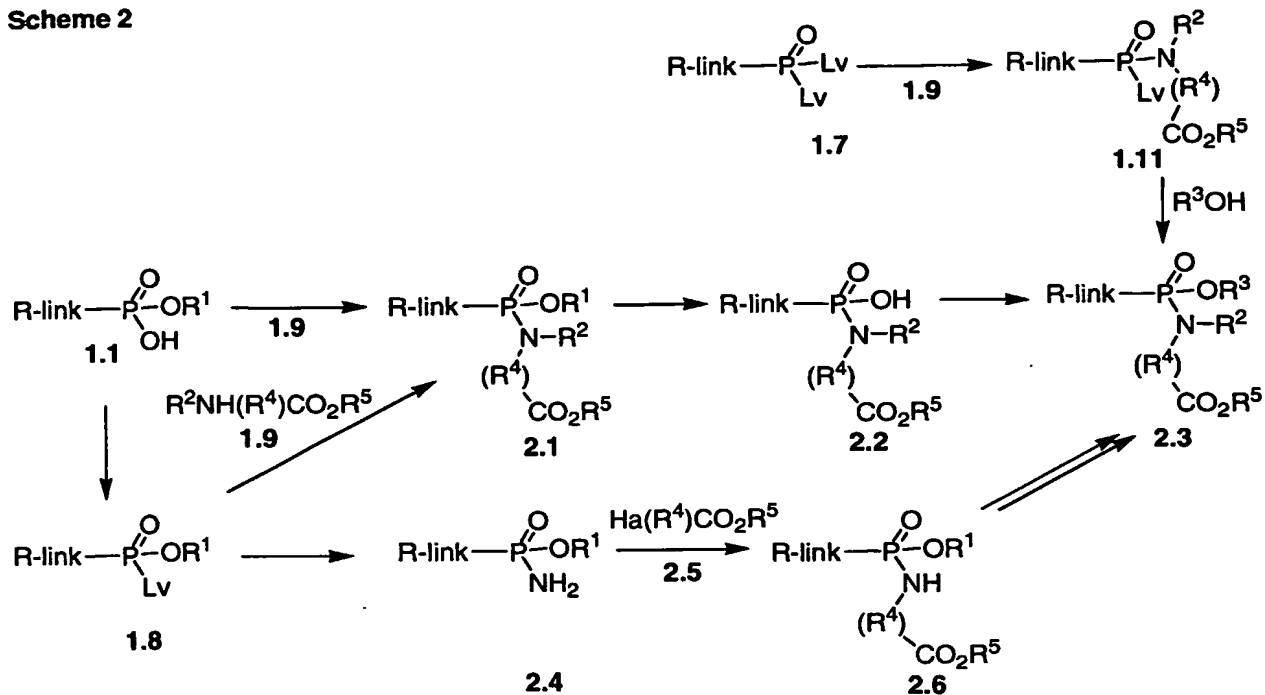
The method is illustrated in Scheme 2, Example 5. In this method, the phosphoryl dichloride **2.22** is reacted in dichloromethane solution with one molar equivalent of ethyl N-methyl

15 tyrosinate **2.23** and dimethylaminopyridine, to generate the monoamidate **2.24**. The product is then reacted with phenol **2.25** in dimethylformamide containing potassium carbonate, to yield the ester amidate product **2.26**.
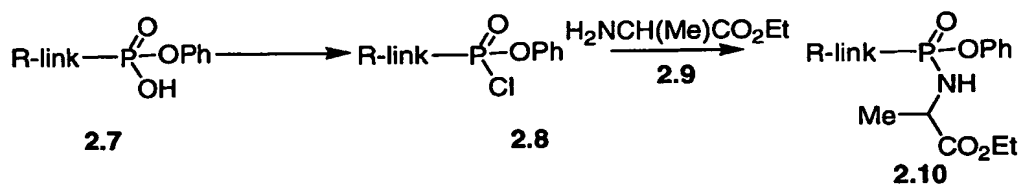
Using these procedures, but employing, in place of ethyl N-methyl tyrosinate **2.23** or phenol

20 **2.25**, the aminoesters **1.9** and/or the hydroxy compounds R^{3}OH, the corresponding products **2.3** are obtained.
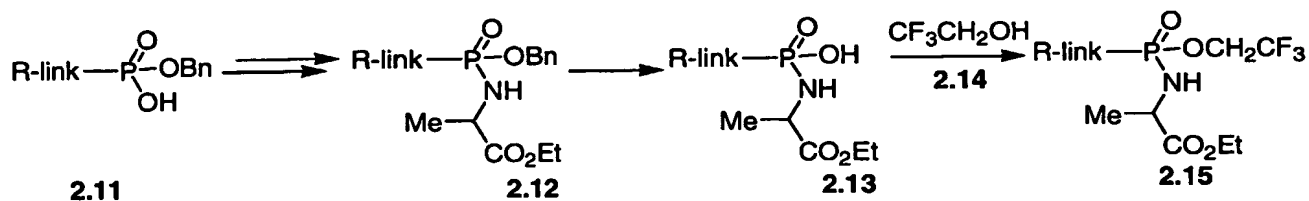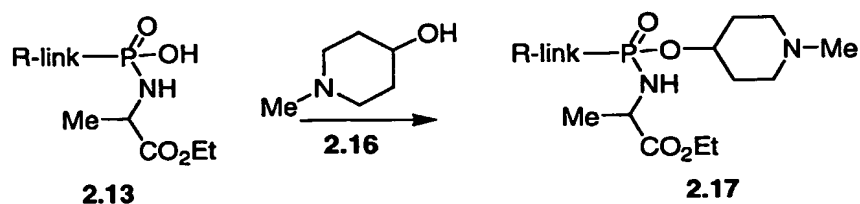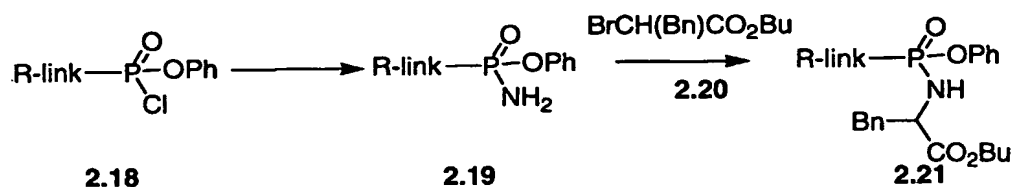
Scheme 2

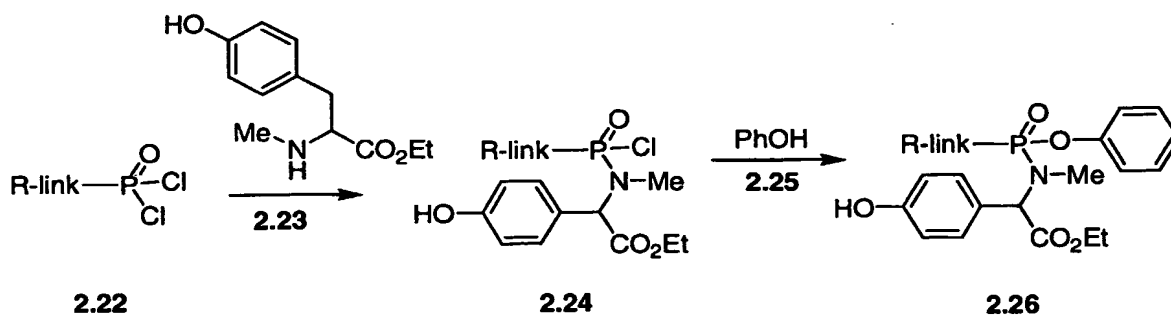**Scheme 2 Example 1**

Scheme 2 Example 2

Scheme 2 Example 3

Scheme 2 Example 4

Scheme 2 Example 5

Scheme 3 illustrates methods for the preparation of carboalkoxy-substituted phosphonate diesters in which one of the ester groups incorporates a carboalkoxy substituent.

5   In one procedure, a phosphonate monoester **1.1**, prepared as described above, is coupled, using one of the methods described above, with a hydroxyester **3.1**, in which the groups R^4 and R^5 are as described in Scheme 1. For example, equimolar amounts of the reactants are coupled in the presence of a carbodiimide such as dicyclohexyl carbodiimide, as described in Aust. J. Chem., 1963, 609, optionally in the presence of dimethylaminopyridine, as described

10   in Tet., 1999, 55, 12997. The reaction is conducted in an inert solvent at ambient temperature.

The procedure is illustrated in Scheme 3, Example 1. In this method, a monophenyl phosphonate **3.9** is coupled, in dichloromethane solution in the presence of dicyclohexyl

15   carbodiimide, with ethyl 3-hydroxy-2-methylpropionate **3.10** to yield the phosphonate mixed diester **3.11**.

Using this procedure, but employing, in place of ethyl 3-hydroxy-2-methylpropionate **3.10**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

20

The conversion of a phosphonate monoester **1.1** into a mixed diester **3.2** is also accomplished by means of a Mitsonobu coupling reaction with the hydroxyester **3.1**, as described in Org. Lett., 2001, 643. In this method, the reactants **1.1** and **3.1** are combined in a polar solvent such as tetrahydrofuran, in the presence of a triarylphosphine and a dialkyl azodicarboxylate,

5   to give the mixed diester **3.2**. The R^1 substituent is varied by cleavage, using the methods described previously, to afford the monoacid product **3.3**. The product is then coupled, for example using methods described above, with the hydroxy compound R^{3}OH, to give the diester product **3.4**.

10   The procedure is illustrated in Scheme 3, Example 2. In this method, a monoallyl phosphonate **3.12** is coupled in tetrahydrofuran solution, in the presence of triphenylphosphine and diethylazodicarboxylate, with ethyl lactate **3.13** to give the mixed diester **3.14**. The product is reacted with tris(triphenylphosphine) rhodium chloride (Wilkinson catalyst) in acetonitrile, as described previously, to remove the allyl group and produce the monoacid product **3.15**. The

15   latter compound is then coupled, in pyridine solution at ambient temperature, in the presence of dicyclohexyl carbodiimide, with one molar equivalent of 3-hydroxypyridine **3.16** to yield the mixed diester **3.17**.

Using the above procedures, but employing, in place of the ethyl lactate **3.13** or 3-

20   hydroxypyridine, a different hydroxyester **3.1** and/or a different hydroxy compound R^{3}OH, the corresponding products **3.4** are obtained.

The mixed diesters **3.2** are also obtained from the monoesters **1.1** via the intermediacy of the activated monoesters **3.5**. In this procedure, the monoester **1.1** is converted into the activated

25   compound **3.5** by reaction with, for example, phosphorus pentachloride, as described in J. Org. Chem., 2001, 66, 329, or with thionyl chloride or oxalyl chloride (Lv = Cl), or with triisopropylbenzenesulfonyl chloride in pyridine, as described in Nucleosides and Nucleotides, 2000, 19, 1885, or with carbonyl diimidazole, as described in J. Med. Chem., 2002, 45, 1284. The resultant activated monoester is then reacted with the hydroxyester **3.1**, as described

30   above, to yield the mixed diester **3.2**.

The procedure is illustrated in Scheme 3, Example 3. In this sequence, a monophenyl phosphonate **3.9** is reacted, in acetonitrile solution at 70°C, with ten equivalents of thionyl

chloride, so as to produce the phosphoryl chloride **3.19**. The product is then reacted with ethyl 4-carbamoyl-2-hydroxybutyrate **3.20** in dichloromethane containing triethylamine, to give the mixed diester **3.21**.

5   Using the above procedures, but employing, in place of ethyl 4-carbamoyl-2-hydroxybutyrate **3.20**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

The mixed phosphonate diesters are also obtained by an alternative route for incorporation of the R^3O group into intermediates **3.3** in which the hydroxyester moiety is already

10   incorporated. In this procedure, the monoacid intermediate **3.3** is converted into the activated derivative **3.6** in which Lv is a leaving group such as chloro, imidazole, and the like, as previously described. The activated intermediate is then reacted with the hydroxy compound R^3OH, in the presence of a base, to yield the mixed diester product **3.4**.

15   The method is illustrated in Scheme 3, Example 4. In this sequence, the phosphonate monoacid **3.22** is reacted with trichloromethanesulfonyl chloride in tetrahydrofuran containing collidine, as described in J. Med. Chem., 1995, 38, 4648, to produce the trichloromethanesulfonyloxy product **3.23**. This compound is reacted with 3-(morpholinomethyl)phenol **3.24** in dichloromethane containing triethylamine, to yield the
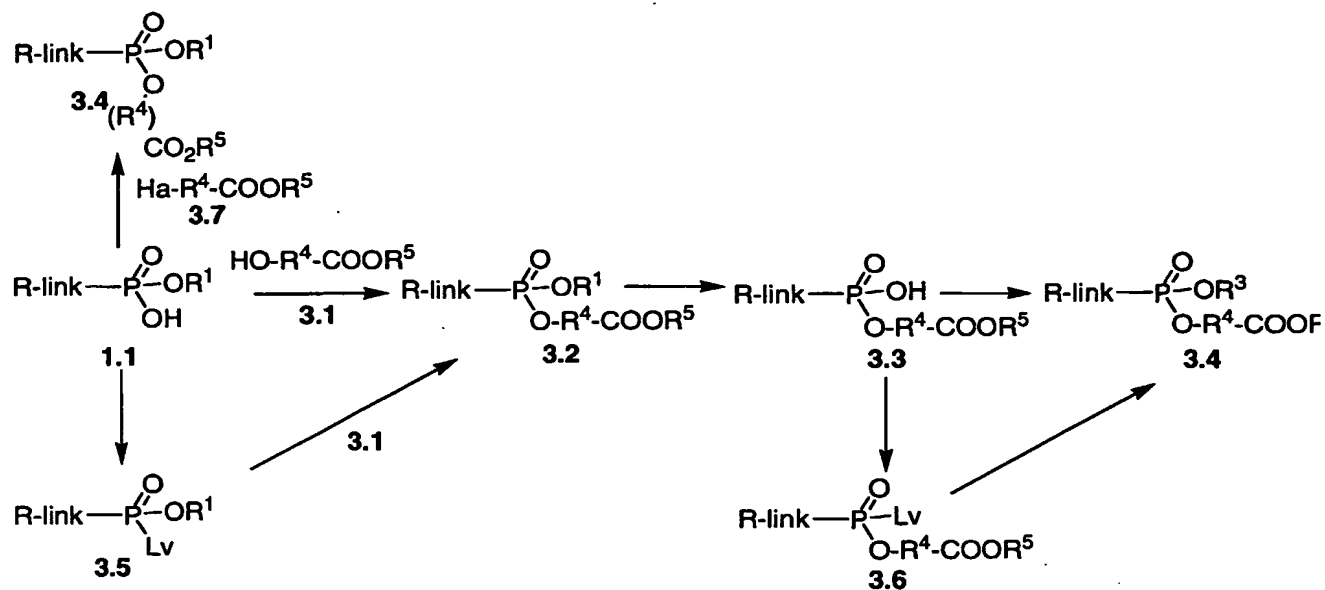
20   mixed diester product **3.25**.

Using the above procedures, but employing, in place of with 3-(morpholinomethyl)phenol **3.24**, different carbinols R^3OH, the corresponding products **3.4** are obtained.

25   The phosphonate esters **3.4** are also obtained by means of alkylation reactions performed on the monoesters **1.1**. The reaction between the monoacid **1.1** and the haloester **3.7** is performed in a polar solvent in the presence of a base such as diisopropylethylamine, as described in Anal. Chem., 1987, 59, 1056, or triethylamine, as described in J. Med. Chem., 1995, 38, 1372, or in a non-polar solvent such as benzene, in the presence of 18-crown-6, as

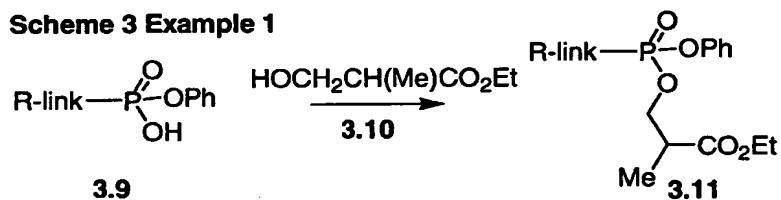30   described in Syn. Comm., 1995, 25, 3565.

The method is illustrated in Scheme **3**, Example **5**. In this procedure, the monoacid **3.26** is reacted with ethyl 2-bromo-3-phenylpropionate **3.27** and diisopropylethylamine in dimethylformamide at 80°C to afford the mixed diester product **3.28**.

5   Using the above procedure, but employing, in place of ethyl 2-bromo-3-phenylpropionate **3.27**, different haloesters **3.7**, the corresponding products **3.4** are obtained.
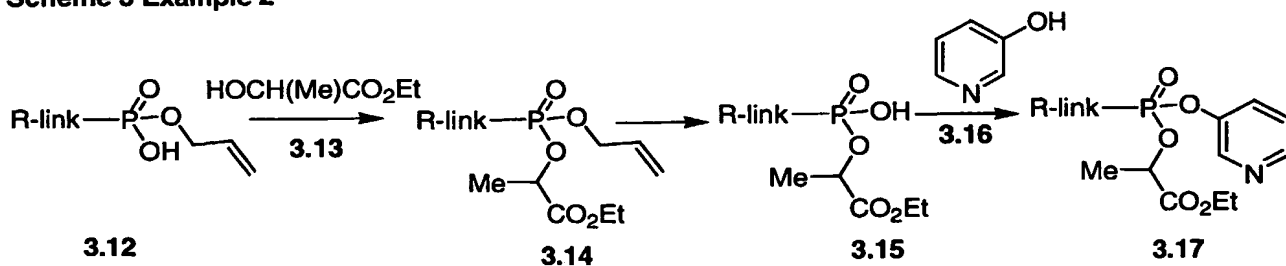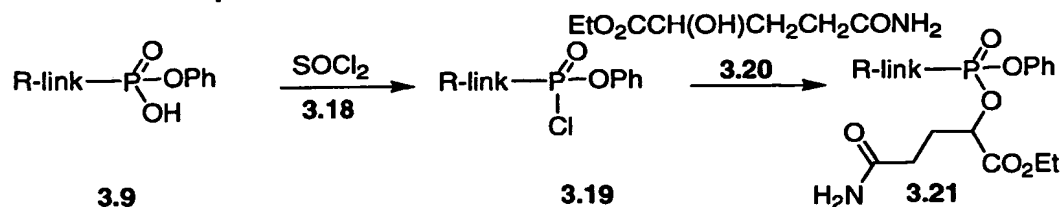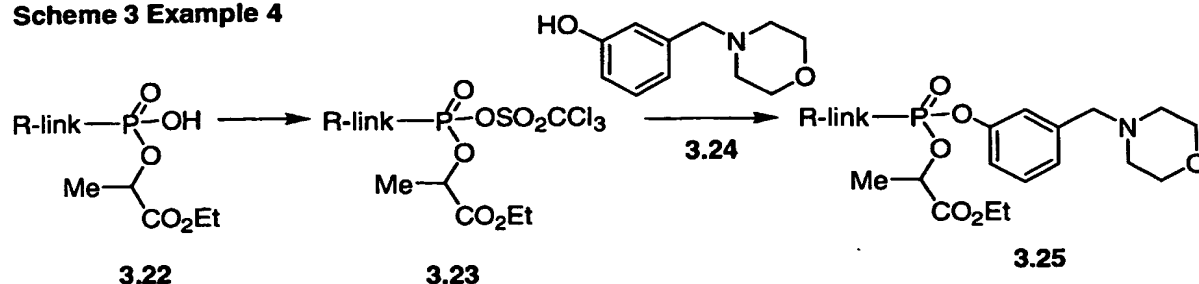
Scheme 3

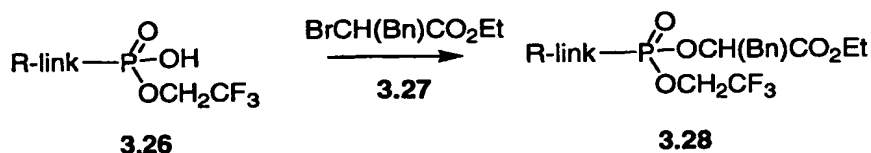**Scheme 3 Example 1**

Scheme 3 Example 2

Scheme 3 Example 3

Scheme 3 Example 4

Scheme 3 Example 5

Scheme **4** illustrates methods for the preparation of phosphonate diesters in which both the

5   ester substituents incorporate carboalkoxy groups.

The compounds are prepared directly or indirectly from the phosphonic acids **1.6**. In one

alternative, the phosphonic acid is coupled with the hydroxyester **4.2**, using the conditions

described previously in Schemes **1 - 3**, such as coupling reactions using dicyclohexyl

10   carbodiimide or similar reagents, or under the conditions of the Mitsonobu reaction, to afford

the diester product **4.3** in which the ester substituents are identical.

This method is illustrated in Scheme **4**, Example **1**. In this procedure, the phosphonic acid **1.6**

is reacted with three molar equivalents of butyl lactate **4.5** in the presence of Aldrithiol-2 and

15   triphenyl phosphine in pyridine at ca. 70°C, to afford the diester **4.6**.

Using the above procedure, but employing, in place of butyl lactate **4.5**, different

hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

Alternatively, the diesters **4.3** are obtained by alkylation of the phosphonic acid **1.6** with a

20   haloester **4.1**. The alkylation reaction is performed as described in Scheme **3** for the

preparation of the esters **3.4**.

This method is illustrated in Scheme 4, Example 2. In this procedure, the phosphonic acid 1.6 is reacted with excess ethyl 3-bromo-2-methylpropionate 4.7 and diisopropylethylamine in dimethylformamide at ca. 80°C, as described in Anal. Chem., 1987, 59, 1056, to produce the diester 4.8.

5   Using the above procedure, but employing, in place of ethyl 3-bromo-2-methylpropionate 4.7, different haloesters 4.1, the corresponding products 4.3 are obtained.


The diesters 4.3 are also obtained by displacement reactions of activated derivatives 1.7 of the phosphonic acid with the hydroxyesters 4.2. The displacement reaction is performed in a polar

10   solvent in the presence of a suitable base, as described in Scheme 3. The displacement reaction is performed in the presence of an excess of the hydroxyester, to afford the diester product 4.3 in which the ester substituents are identical, or sequentially with limited amounts of different hydroxyesters, to prepare diesters 4.3 in which the ester substituents are different. The methods are illustrated in Scheme 4, Examples 3 and 4. As shown in Example 3, the

15   phosphoryl dichloride 2.22 is reacted with three molar equivalents of ethyl 3-hydroxy-2-(hydroxymethyl)propionate 4.9 in tetrahydrofuran containing potassium carbonate, to obtain the diester product 4.10.

Using the above procedure, but employing, in place of ethyl 3-hydroxy-2-(hydroxymethyl)propionate 4.9, different hydroxyesters 4.2, the corresponding products 4.3

20   are obtained.

Scheme 4, Example 4 depicts the displacement reaction between equimolar amounts of the phosphoryl dichloride 2.22 and ethyl 2-methyl-3-hydroxypropionate 4.11, to yield the monoester product 4.12. The reaction is conducted in acetonitrile at 70°C in the presence of diisopropylethylamine. The product 4.12 is then reacted, under the same conditions, with one

25   molar equivalent of ethyl lactate 4.13, to give the diester product 4.14.

Using the above procedures, but employing, in place of ethyl 2-methyl-3-hydroxypropionate 4.11 and ethyl lactate 4.13, sequential reactions with different hydroxyesters 4.2, the corresponding products 4.3 are obtained.
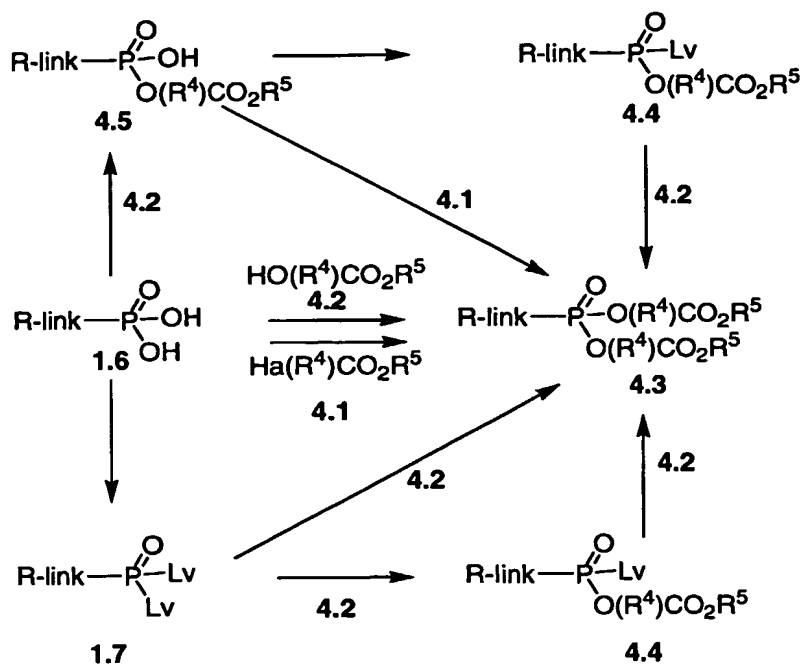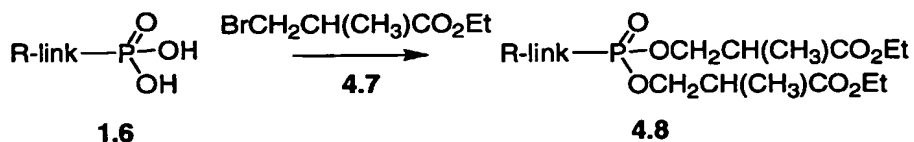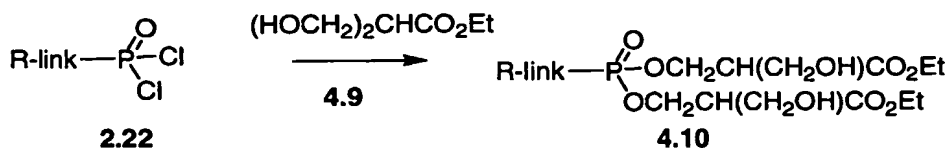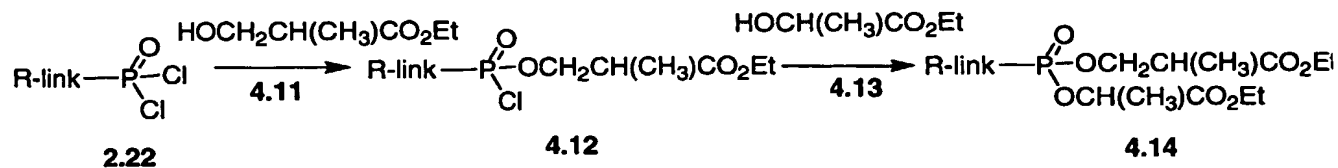
Scheme 4
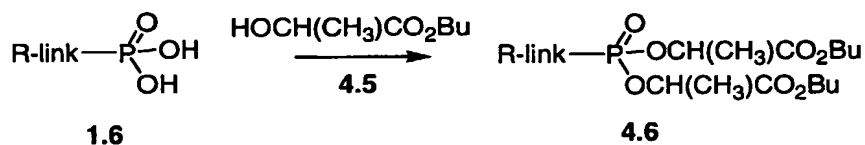
Scheme 4 Example 1

Scheme 4 Example 2

Scheme 4 Example 3

Scheme 4 Example 4

Aryl halides undergo Ni^{+2} catalyzed reaction with phosphite derivatives to give aryl phosphonate containing compounds (Balthazar, et al (1980) *J. Org. Chem.* 45:5425). Phosphonates may also be prepared from the chlorophosphonate in the presence of a palladium catalyst using aromatic triflates (Petrakis, et al, (1987) *J. Am. Chem. Soc.* 109:2831;

5   Lu, et al, (1987) *Synthesis*, 726). In another method, aryl phosphonate esters are prepared from aryl phosphates under anionic rearrangement conditions (Melvin (1981) *Tetrahedron Lett.* 22:3375; Casteel, et al, (1991) *Synthesis*, 691). N-Alkoxy aryl salts with alkali metal derivatives of cyclic alkyl phosphonate provide general synthesis for heteroaryl-2-phosphonate linkers (Redmore (1970) *J. Org. Chem.* 35:4114). These above mentioned methods can also

10   be extended to compounds where the W^5 group is a heterocycle. Cyclic-1,3-propanyl prodrugs of phosphonates are also synthesized from phosphonic diacids and substituted propane-1,3-diols using a coupling reagent such as 1,3-dicyclohexylcarbodiimide (DCC) in presence of a base (e.g., pyridine). Other carbodiimide based coupling agents like 1,3-disopropylcarbodiimide or water soluble reagent, 1-(3-dimethylaminopropyl)-3-

15   ethylcarbodiimide hydrochloride (EDCI) can also be utilized for the synthesis of cyclic phosphonate prodrugs.

The carbamoyl group may be formed by reaction of a hydroxy group according to the methods known in the art, including the teachings of Ellis, US 2002/0103378 A1 and Hajima, US Patent No. 6018049.

20   Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically

25   consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20°C), although for metal hydride reductions frequently the temperature is reduced to 0°C to -100°C, solvents are typically aprotic for reductions and may be either

30   protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0°C to -100°C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (e.g. inert gas environments) are common in the art and will be applied when applicable.

General synthetic routes to substituted imidazoles are well established. See Ogata M (1988) *Annals of the New York Academy of Sciences* 544:12-31; Takahashi et al (1985) *Heterocycles* 23:6, 1483-1492; Ogata et al (1980) *CHEM IND LONDON* 2:5-86; Yanagisawa et al US Patent No. 5646171; Rachwal et al US 2002/0115693 A1; Carlson et al US Patent Nos. 3790593; 3761491 and 3773781; Aono et al US Patent No. 6054591; Hajima et al US Patent No. 6057448; Sugimoto et al EP 00552060 and US Patent No. 5326780.
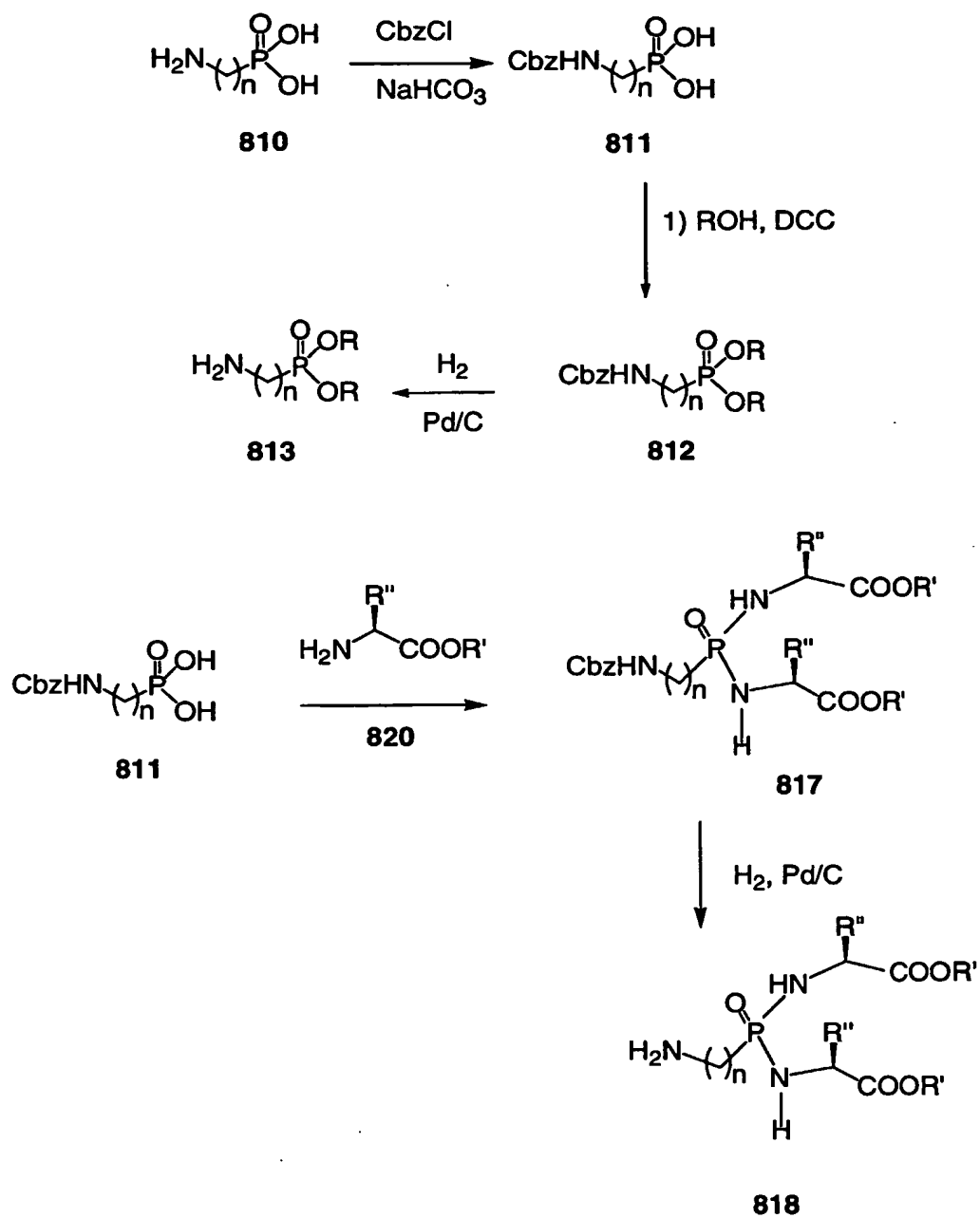
Amino alkyl phosphonate compounds **809**:

809
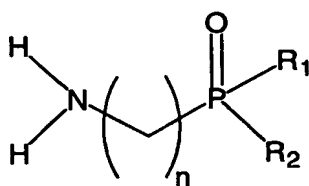
are a generic representative of compounds **811, 813, 814, 816** and **818** (Scheme 2). The alkylene chain may be any length from 1 to 18 methylene groups (n = 1-18). Commercial amino phosphonic acid **810** was protected as carbamate **811**. The phosphonic acid **811** was converted to phosphonate **812** upon treatment with ROH in the presence of DCC or other conventional coupling reagents. Coupling of phosphonic acid **811** with esters of amino acid **820** provided bisamidate **817**. Conversion of acid **811** to bisphenyl phosphonate followed by hydrolysis gave mono-phosphonic acid **814** (Cbz = $C_6H_5CH_2C(O)-$), which was then transformed to mono-phosphonic amidate **815**. Carbamates **813, 816** and **818** were converted to their corresponding amines upon hydrogenation. Compounds **811, 813, 814, 816** and **818** are useful intermediates to form the phosphonate compounds of the invention.

Scheme 2

Following the similar procedures, replacement of amino acid esters **820** with lactates
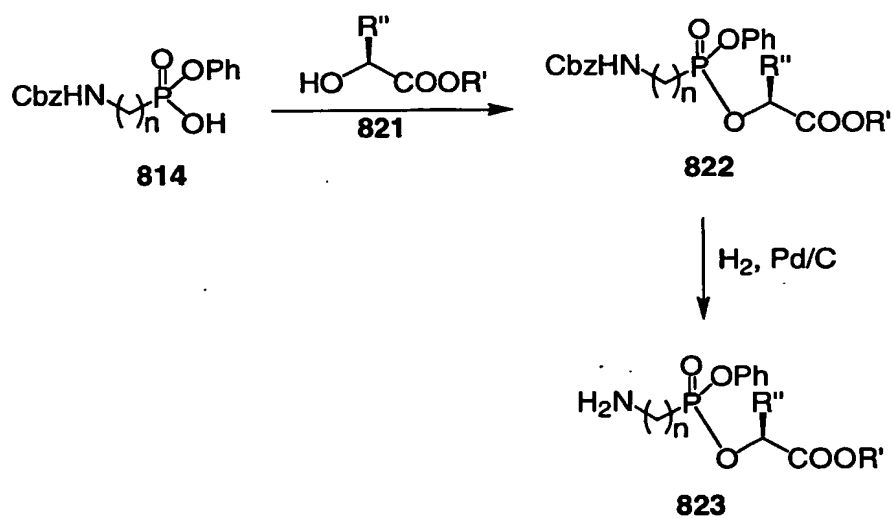
821 (Scheme 3) provides mono-phosphonic lactates **823**. Lactates **823** are useful

intermediates to form the phosphonate compounds of the invention.

Scheme 3

Examples General Section

The following Examples refer to the Schemes. Some Examples have been performed multiple times. In repeated Examples, reaction conditions such as time, temperature, concentration and the like, and yields were within normal experimental ranges. In repeated
5   Examples where significant modifications were made, these have been noted where the results varied significantly from those described. In Examples where different starting materials were used, these are noted. When the repeated Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl ester", this intends that an otherwise present group, in this case typically a methyl ester, is taken to be the same group modified as indicated.

10   Example 1

To a solution of 2-aminoethylphosphonic acid (810 where n =2, 1.26 g, 10.1 mmol) in 2N NaOH (10.1 mL, 20.2 mmol) was added benzyl chloroformate (1.7 mL, 12.1 mmol). See Scheme 5. After the reaction mixture was stirred for 2 d at room temperature, the mixture was partitioned between Et_2O and water. The aqueous phase was acidified with 6N HCl until
15   pH = 2. The resulting colorless solid was dissolved in MeOH (75 mL) and treated with Dowex 50WX8-200 (7 g). After the mixture was stirred for 30 minutes, it was filtered and evaporated under reduced pressure to give carbamate 28 (2.37 g, 91%) as a colorless solid.

To a solution of carbamate 28 (2.35 g, 9.1 mmol) in pyridine (40 mL) was added phenol (8.53 g, 90.6 mmol) and 1,3-dicyclohexylcarbodiimide (7.47 g, 36.2 mmol). After the
20   reaction mixture was warmed to 70°C and stirred for 5 h, the mixture was diluted with CH_3CN and filtered. The filtrate was concentrated under reduced pressure and diluted with EtOAc. The organic phase was washed with sat. NH_4Cl, sat. $NaHCO_3$, and brine, then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel twice (eluting 40-60% EtOAc/hexane) to give phosphonate 29
25   (2.13 g, 57%) as a colorless solid.

To a solution of phosphonate 29 (262 mg, 0.637 mmol) in iPrOH (5 mL) was added TFA (0.05 mL, 0.637 mmol) and 10% Pd/C (26 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 1 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give amine 30 (249 mg, 100%) as a colorless oil
30   (Scheme 5).

Following the similar procedures, replacement of amino acid esters with lactates (Scheme 6) provided mono-phosphonic lactates, e.g. 823.

Scheme 6
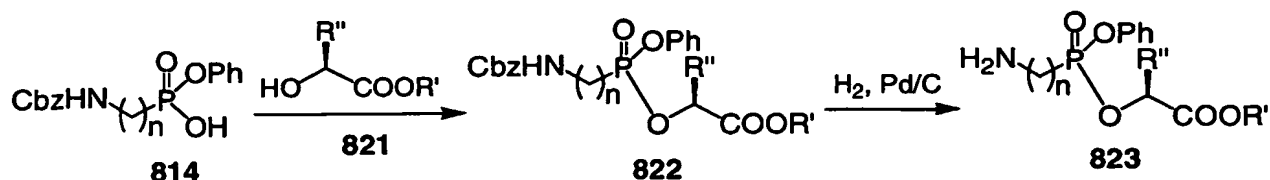
5   Treatment of alcohol **801** (prepared according to literature) with MsCl and TEA

afforded chloride **802** (Scheme 7). Chloride **802** was converted to compound **803** by reacting

with **809**, which preparation is detailed in Schemes 3 and 4, in the presence of base. When

mesylate **802** was treated with NaCN, imidazole nitrile **804** was provided. Reduction of **804**

with DIBAL followed by $NaBH_4$ yielded imidazole alcohol **806**. Repeating the same

10   procedure several times furnished alcohol **807** with the desired length. Hydrolysis of

imidazole nitrile **804** provided acid **805**. Coupling of acid **805** in the presence of conventional

reagents afforded the amide **808**. Phosphorus compound **807'** was produced by transforming

alcohol **807** to its corresponding mesylate followed by treating with amine **809**.

Scheme 7
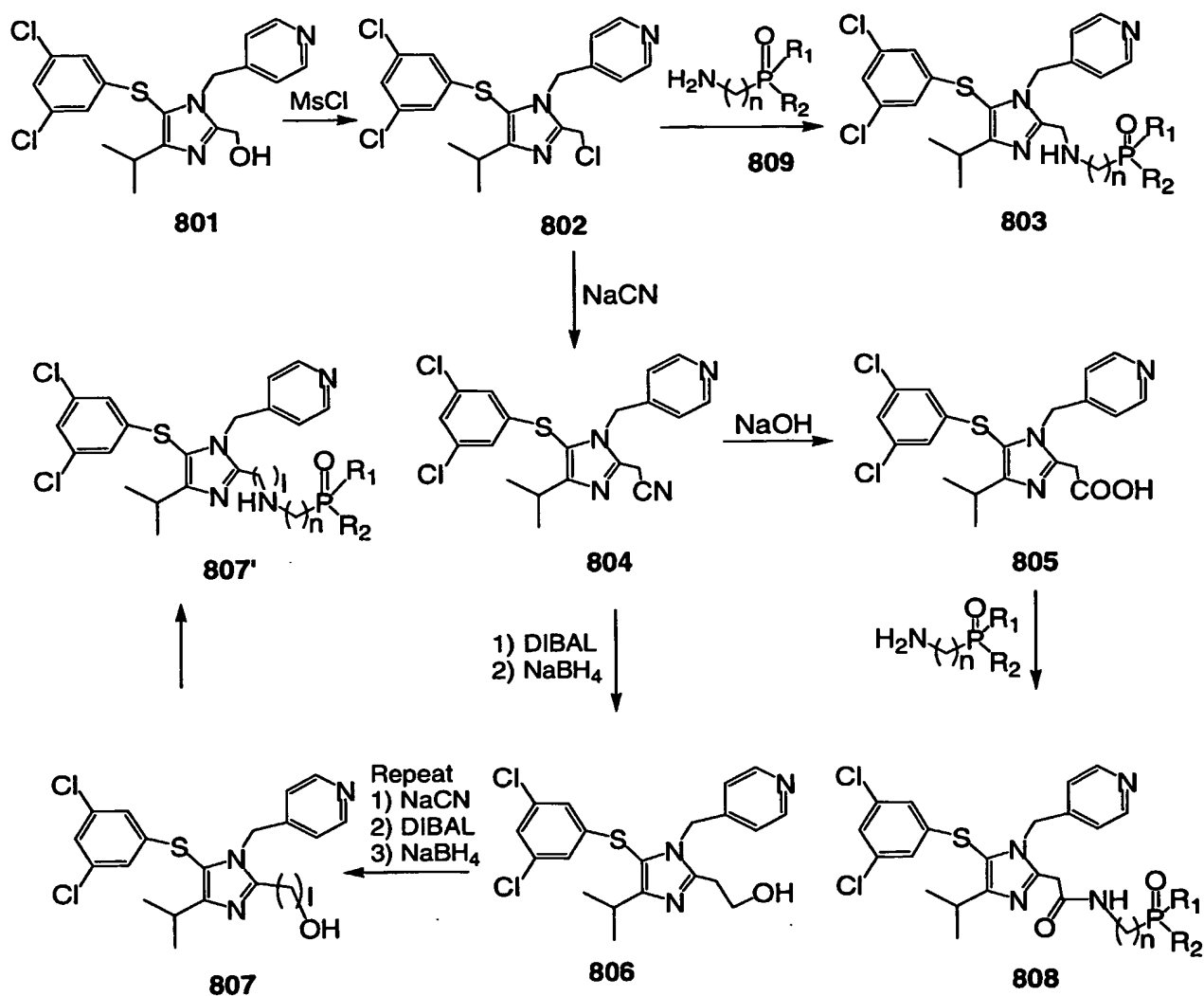
Alcohol **825** was converted to bromide **826** by first transformed to its mesylate and then treated with NaBr, this conversion was also realized by reacting alcohol **825** with Ph₃P and CBr₄ (Scheme 8). Upon treating with P(OR)₃, phosphonate **827** was produced. Esters was then removed to form acid, and following the similar procedure described in Scheme 2 and 3, desired phosphonate, bisphosphoamidate, mono-phosphoamidate, and monophospholactate were produced.

Scheme 8

825

MsCl; NaBr

or

CBr₄, Ph₃P

826

P(OR)₃

827

TMSBr

CH₃CN

828

829
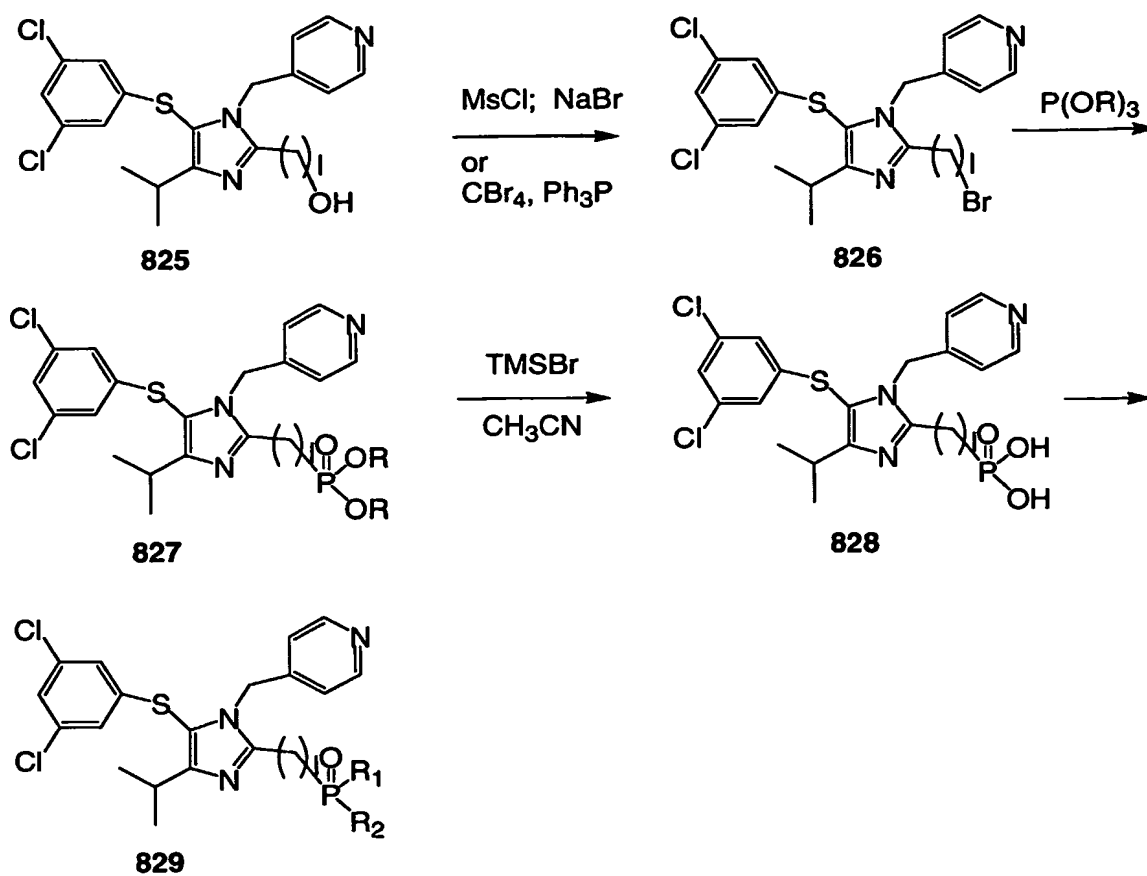
5   In Scheme 9, alcohol **830** was converted to carbonate **831** by reacting with either p-nitrophenyl chloroformate or p-nitrophenyl carboxy anhyride. Treatment of carbonate **831** with amine **809** in the presence of suitable base afforded desired phosphonate compounds **832**.

Scheme 9
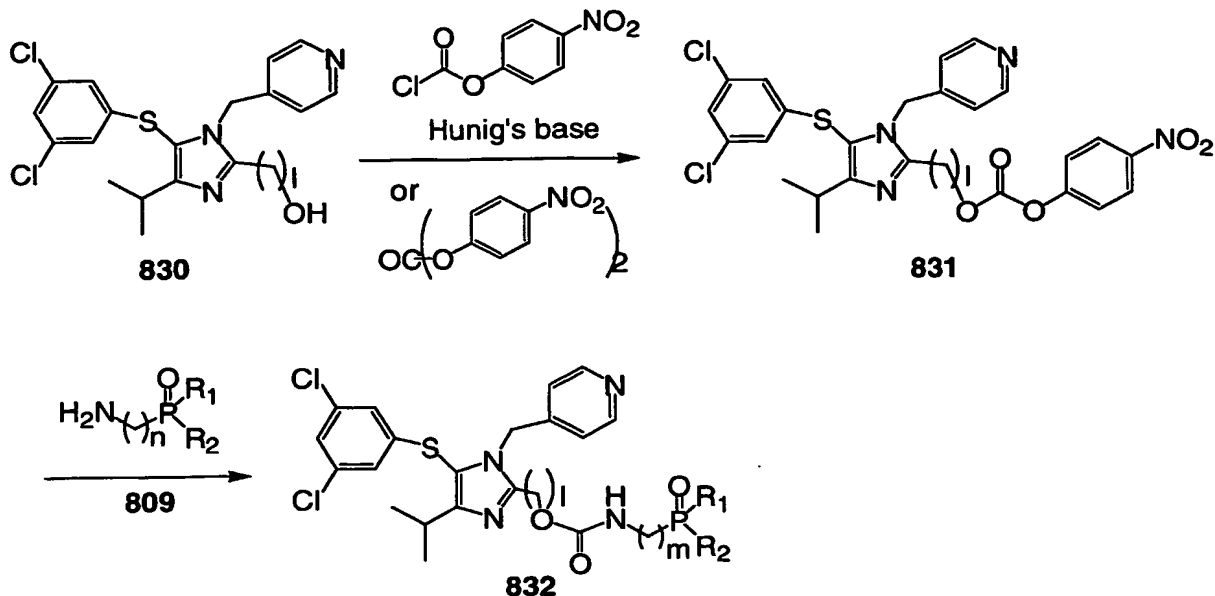
Phosphorus compound **838** was produced according to the procedures described in Scheme 10. Replacement of chloride group in compound **833** with azide followed by reduction with triphenylphosphine provided amine **834**. Replacement of chloride group in compound **833** with cyanide, e.g. sodium cyanide, provided amine **835**. Reduction of nitrile **835** furnished amine **836**. Reaction of amines, e.g. **834** or **836**, with triflate **841** in the presence of a base afforded phosphonate **837**. Removal of benzyl group of **837** gave its corresponding phosphonic acid, e.g. **838** where $R_1 = H$, which was converted to various phosphorus compounds according to the procedure described in the previous Schemes.

Scheme 10
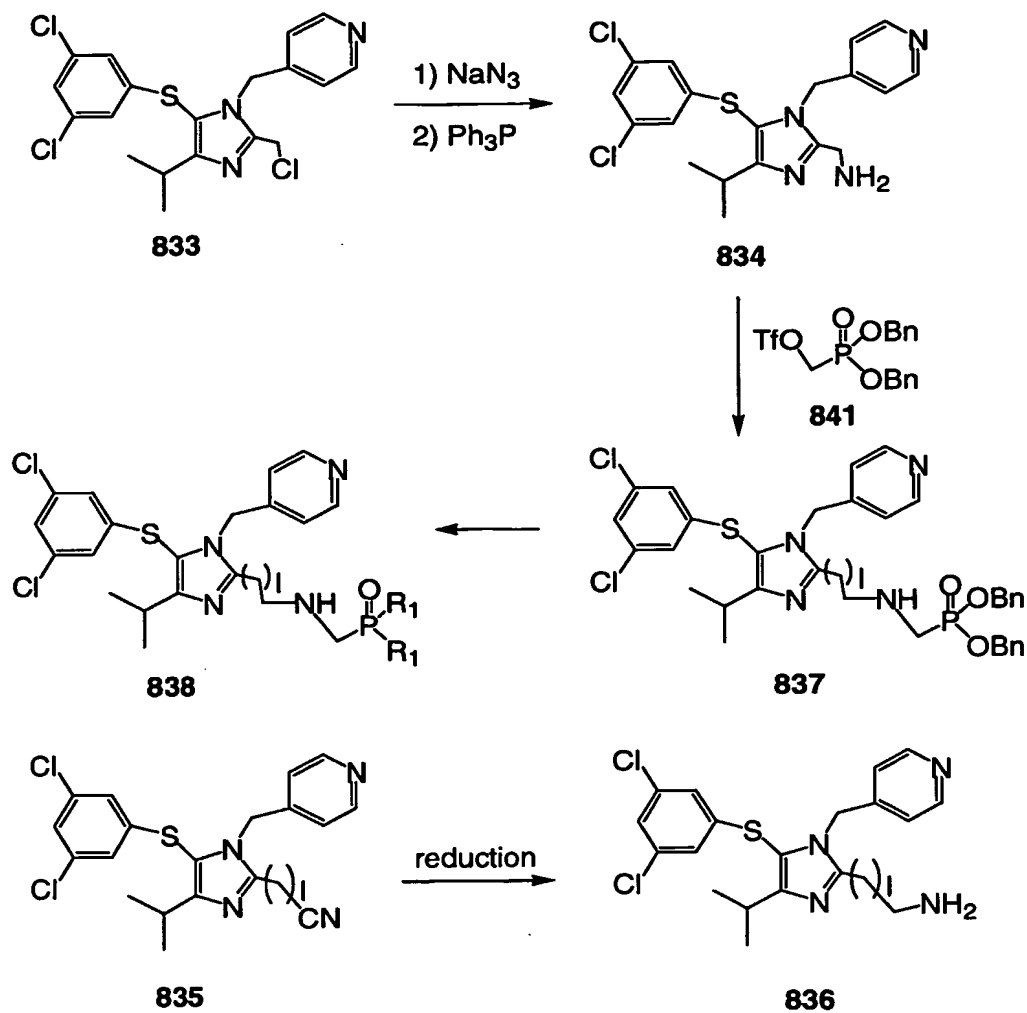
Phosphorus compound **840** was produced in a similar way as described in Scheme 10 except by replacing amines with alcohols **801**, or generally, **807** (Scheme 11).

Scheme 11
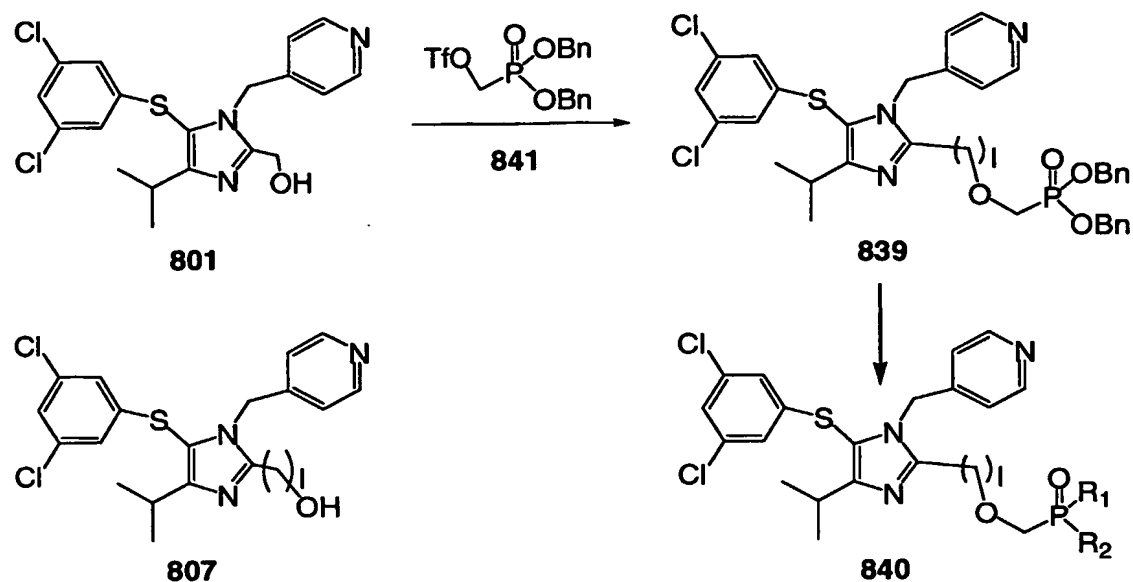
5   Phosphorus compound 848 was synthesized according to procedures described in
Scheme 12. Iodoimidazole 842 was converted to imidazole phenyl thioether 843 by reacting
with LiH and substituted phenyl disulfide (Scheme 12). Treatment of imidazole with NaH and
4-picolyl chloride gave imidazole 844. Benzyl and methyl groups were removed by treating
with strong acid to provide alcohol 845. Conversion of phenol 845 to phosphonate 846 was
10   accomplished by reacting phenol 845 with triflate 841 in the presence of base. Alcohol 846
was reacting with trichloroacetyl isocyanate followed by treatment of alumina afforded
carbamate 847. Phosphonate 847 was transformed to all kinds of phosphorus compound 848
followed the procedure described for 838 in Scheme 10.

Scheme 12

5
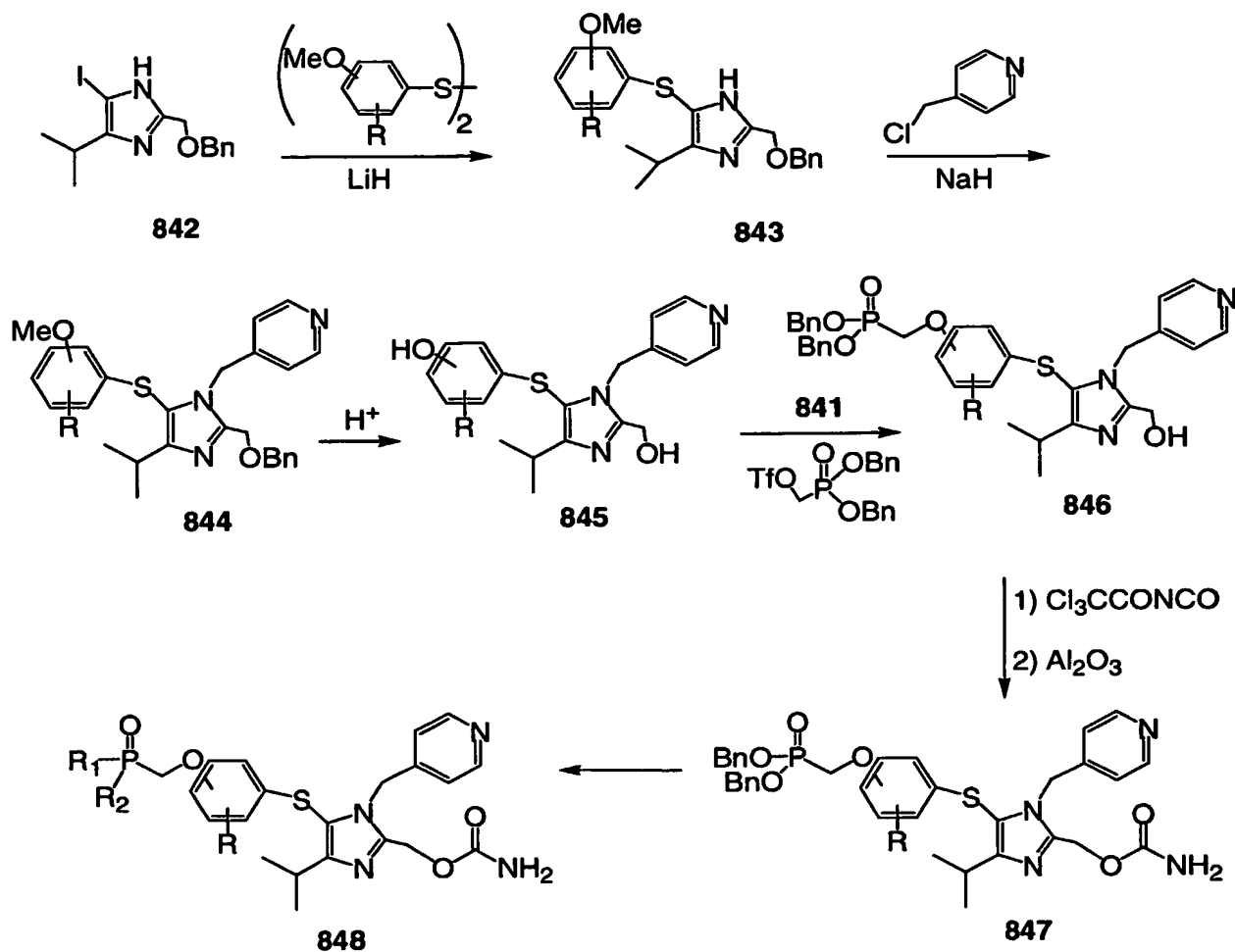
Phosphorus compound **854** was prepared as shown in Scheme 13. Imidazole **849** (prepared according to US Patent Nos. 5910506 and 6057448) was converted to **850** by reacting with chloride in the presence of base. Benzyl and methyl groups were removed by treating ether **850** with strong protonic or Lewis acid to furnish phenol **851**. Treatment of

10   phenol **851** with base followed by triflate **841** gave phosphonate **852**. Following similar procedures described in Scheme 12 transforming alcohol **846** to phosphorus compound **848**, alcohol **852** was converted to phosphorus compound **854**.

Scheme 13

849 → **850** → **851** → **852** → **853** → **854**

841

X = N, CH
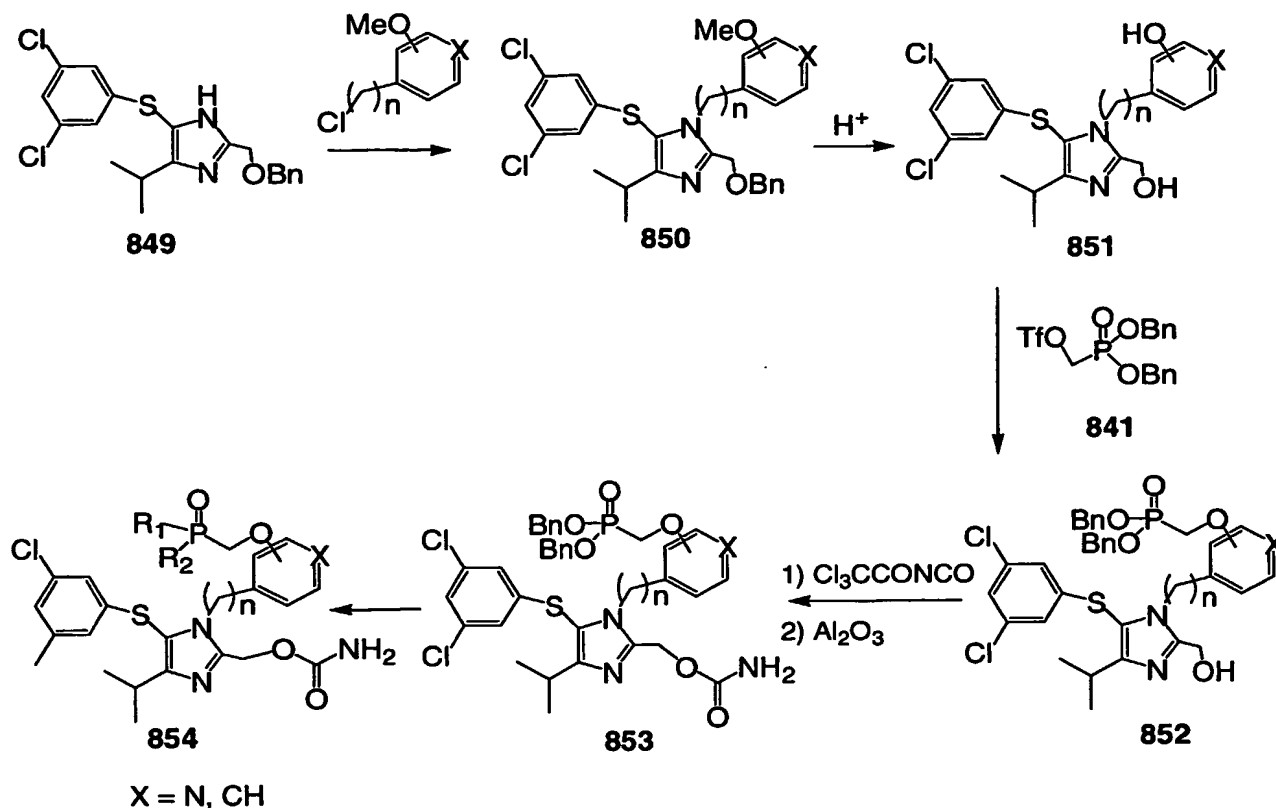
5   Preparation of phosphorus compound **861** is shown in Scheme 14. Imidazole **855** was synthesized by treating compound **842** with NaH followed by allyl bromide. Hydroboration followed by oxidative work up gave alcohol **856**. Ozonolysis followed by reduction of the resulting aldehyde afforded alcohol **857**. Alcohol **858**, which has variation of length, was obtained by following the same transformation of alcohol **806** to **807** as exhibited in Scheme 7.

10   Mitsunobu reaction of alcohol **859** with substituted phenols gave imidazole **860**. Phenol ether ·860 was converted to phosphonate **861** by following same procedure of transforming compound **850** to **854** as described in Scheme 13.

Scheme 14
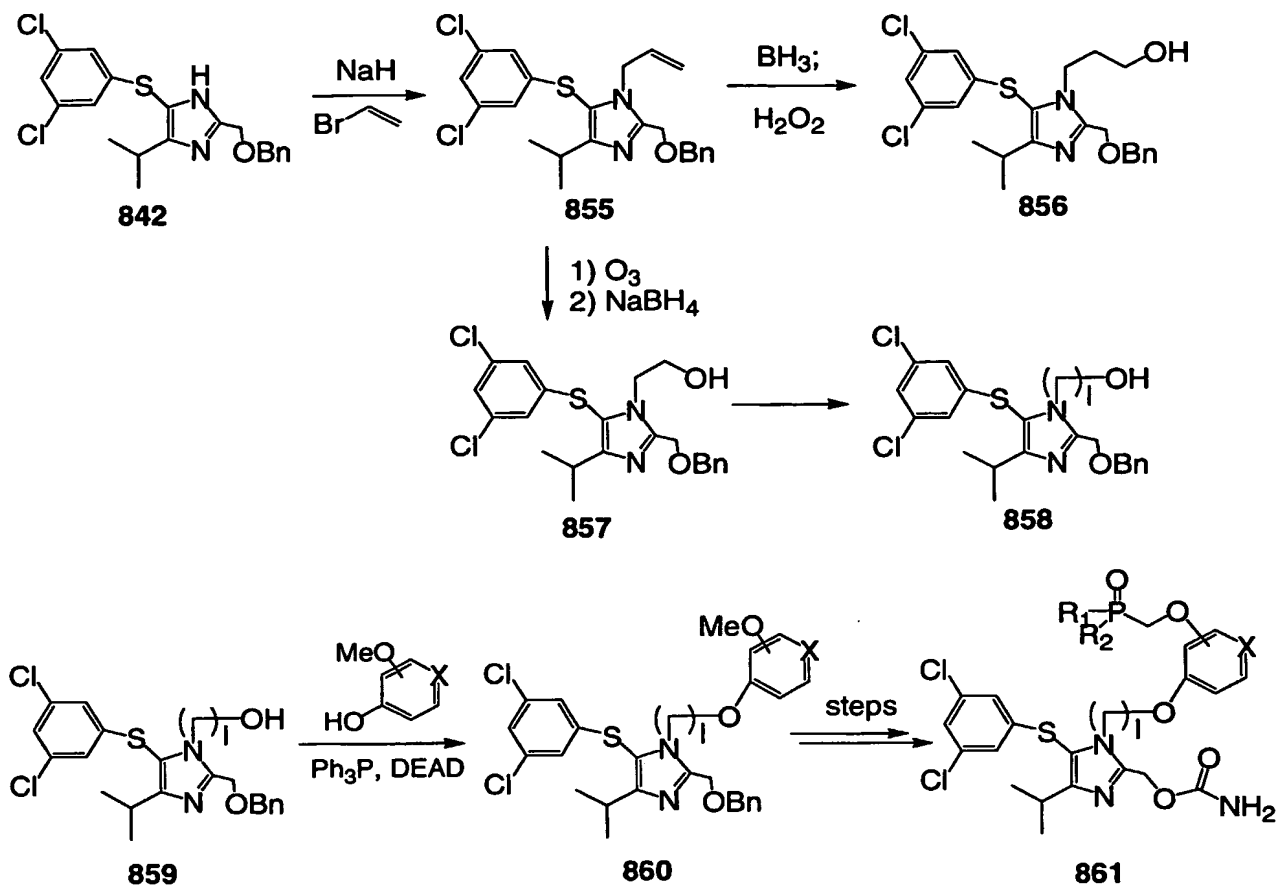
5

In Scheme 15, preparation of phosphorus compounds **864** is shown. Alcohol **858** was converted to mesylate **862** by reacting with MsCl. Removal of benzyl group, followed by conversion of the resultant alcohol to the corresponding carbamate (described in previous Schemes) furnished compound **863**. Substitution of mesylate with amine **809** generated

10   phosphorus compound **864**.

Scheme 15

858 → 862 → (864)

863

809

864
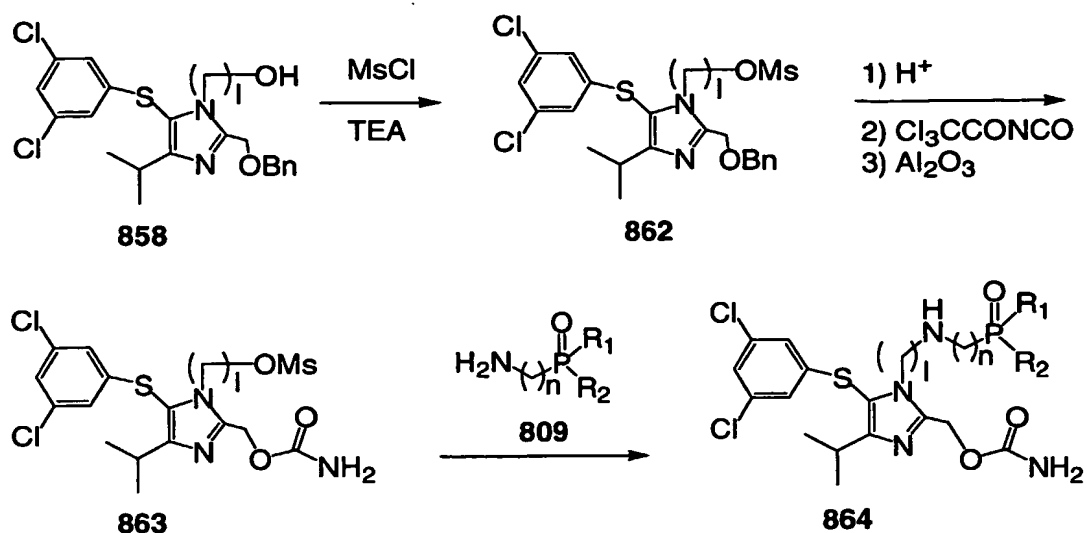
Synthesis of phosphorus compound **866** is described in Scheme 16. Protection of

alcohol **858** to its acetate **865**, followed by the conversion of the benzyl, —OBn group to the

corresponding carbamate as described for transforming compound **862** to **863** in Scheme 15,

gave compound **865**. Hydrolysis of acetate, and treatment of the resultant alcohol with triflate

841 in the presence of base afforded phosphonate **866**.

Scheme 16

858   865   841   866
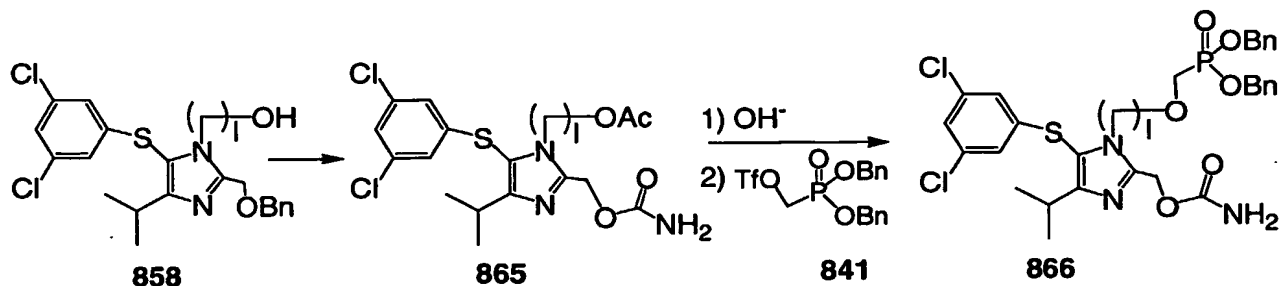
Scheme 17 describes synthesis of phosphorus compound **672**. Mesylate **862** was

transformed to bromide **867** by reacting with NaBr. Arbusov reaction gave phosphonate **868**.

Both benzyl and ethyl groups were cleaved when treated with TMSBr to yield compound **869**.

Coupling of phosphonic acid **869** with PhOH provided bisphenyl phosphonate **670**.

Compound **670** was converted to various phosphorus compounds **671** according to the

procedures described in Schemes 1, 2 and 3. Phosphorus compound **672** was obtained by

repeating the procedures shown before.
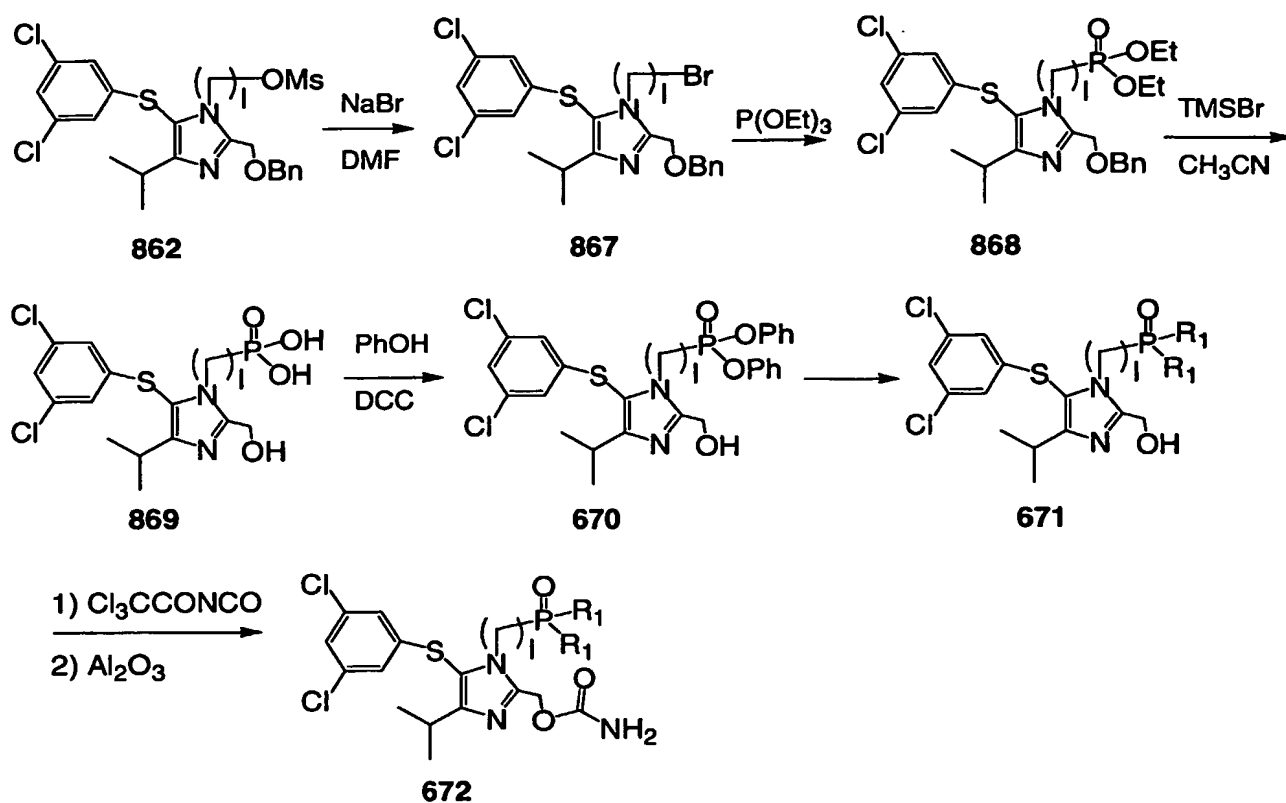
Scheme 17

Scheme 18
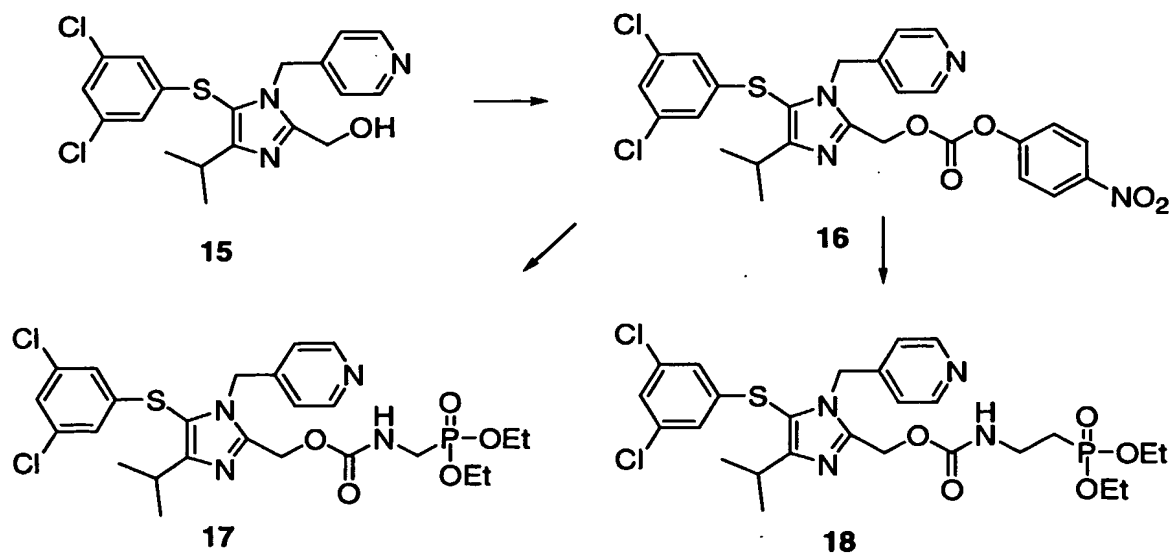
Example 10

16
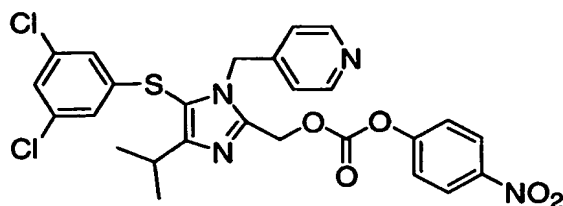
To a solution of alcohol **15** (42 mg, 0.10 mmol) in CH_2Cl_2 (5 mL) was added
triethylamine (24 µL, 0.17 mmol) and bis(4-nitrophenyl) carbonate (46 mg, 0.15 mmol). See
Scheme 18. After the reaction mixture was stirred for 4 h at room temperature, the mixture
was partitioned between CH_2Cl_2 and water. The organic phase was dried over Na_2SO_4,
filtered, and evaporated under reduced pressure. The crude product was chromatographed on
silica gel (eluting 60-70% EtOAc/hexane) to give carbonic acid 5-(3,5-dichloro-
phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethyl ester 4-nitro-phenyl
ester **16** (47 mg, 82%) as a colorless oil.

Example 11A
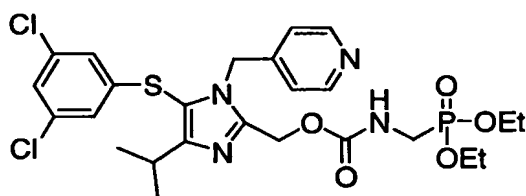
17

To a solution of carbonate **16** (14 mg, 0.024 mmol) in CH_3CN (2 mL) was added
diethyl(aminomethyl)phosphonate (10 mg, 0.037 mmol) and diisopropylethylamine (8 µL,
0.048 mmol). See Scheme 18. After the reaction mixture was stirred for 16 h at room
temperature, the mixture was concentrated under reduced pressure. The residue was purified
by preparative thin layer chromatography (eluting 5% MeOH/CH_2Cl_2) to give {[5-(3,5-
dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-
ylmethoxycarbonylamino]-methyl}-phosphonic acid diethyl ester **17** (13 mg, 90%) as a pale
yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, 2H), 7.04 (t, 1H), 6.78 (d, 2H), 6.68 (d,
2H), 5.25 (s, 2H), 5.19 (s, 2H), 4.98 (bt, 1H), 4.11 (dq, 4H), 3.49 (ABq, 2H), 3.17 (dq, 1H),
1.30 (m, 12H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 21.9.

Example 11B

18
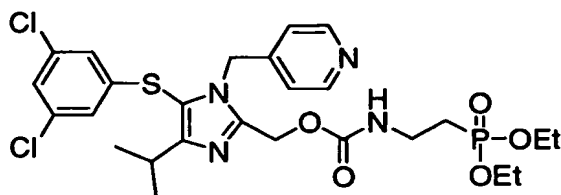
To a solution of carbonate **16** (82 mg, 0.143 mmol) in CH₃CN (5 mL) was added
diethyl(aminoethyl)phosphonate (58 mg, 0.214 mmol) and diisopropylethylamine (0.05 mL,
0.286 mmol). See Scheme 20. After the reaction mixture was stirred for 16 h at room
temperature, the mixture was concentrated under reduced pressure. The residue was
chromatographed on silica gel (eluting 5-7.5% MeOH/CH₂Cl₂) to give {2-[5-(3,5-Dichloro-
phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonylamino]-
ethyl}-phosphonic acid diethyl ester **18** (79 mg, 90%) as a pale yellow oil. ¹H NMR (300
MHz, CDCl₃) δ 8.43 (d, 2H), 7.02 (s, 1H), 6.77 (d, 2H), 6.67 (s, 2H), 5.32 (t, 1H), 5.24 (s,
2H), 5.16 (s, 2H), 4.08 (m, 4H), 3.35 (m, 2H), 3.15 (m, 1H), 1.86 (m, 2H), 1.30 (m, 6H),
1.29 (s, 6H). ³¹P NMR (300 MHz, CDCl₃) δ 31.5.

Scheme 19

Example 11C

23
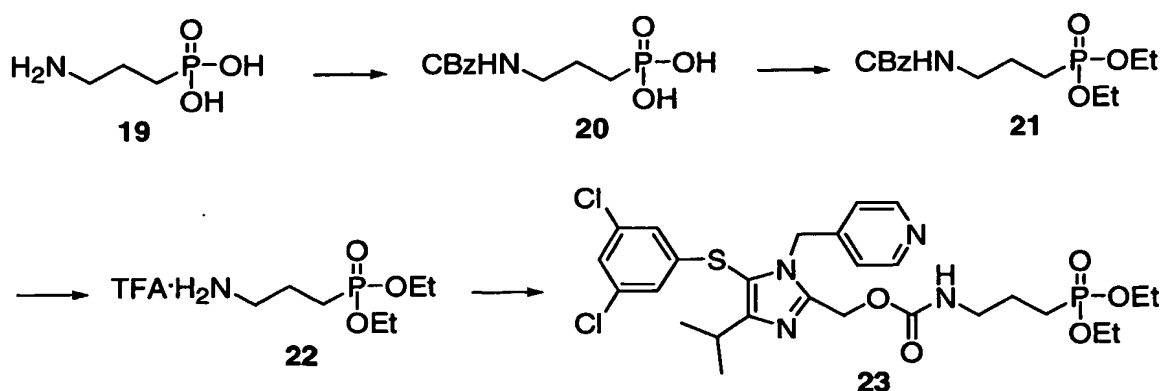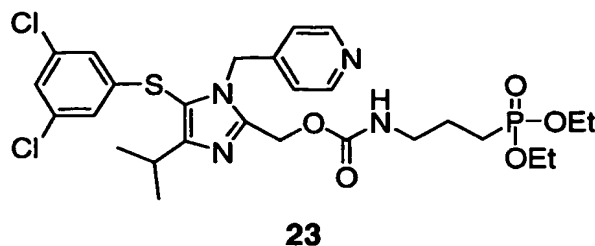
To a solution of 3-aminopropylphosphonic acid **19** (500 g, 3.59 mmol) in 2N NaOH (3.6 mL, 7.19 mmol) was added benzyl chloroformate (0.62 mL, 4.31 mmol) according to Scheme 19. After the reaction mixture was stirred for 16 hours at room temperature, the mixture was partitioned between Et_2O and water. The aqueous phase was acidified with 6N HCl until pH = 2. The resulting colorless solid was dissolved in MeOH (75 mL) and treated with Dowex 50WX8-200 (2.5 g). After the mixture was stirred for 30 minutes, it was filtered and evaporated under reduced pressure to give carbamate **20** (880 mg, 90%) as a colorless solid.

To a solution of carbamate **20** (246 mg, 0.90 mmol) in benzene (5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene phenol (0.27 mL, 1.8 mmol) and iodoethane (0.22 mL, 2.7 mmol). After the reaction mixture was warmed to 60°C and stirred for 16 h, the mixture was concentrated under reduced pressure and partitioned between EtOAc and sat. NH_4Cl. The crude product was chromatographed on silica gel (eluting 3-4% $MeOH/CH_2Cl_2$) to give phosphonate **21** (56 mg, 19%) as a colorless oil.

To a solution of phosphonate **21** (56 mg, 0.17 mmol) in EtOH (3 mL) was added TFA (13 µL, 0.17 mmol) and 10% Pd/C (11 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 1 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give amine **22** (52 mg, 99%) as a colorless oil.

To a solution of carbonate **16** (15 mg, 0.026 mmol) in CH_3CN (2 mL) was added diethyl(aminopropyl)phosphonate (16 mg, 0.052 mmol) and diisopropylethylamine (11 µL, 0.065 mmol). After the reaction mixture was stirred for 16 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (eluting 5% $MeOH/CH_2Cl_2$) to give {3-[5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonylamino]-propyl}-phosphonic acid diethyl ester **23** (13 mg, 79%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, 2H), 7.04 (t, 1H), 6.80 (d, 2H), 6.68 (d, 2H), 5.26 (s, 2H), 5.18 (s,

2H), 5.08 (bt, 1H), 4.08 (m, 4H), 3.15 (m, 3H), 1.72 (m, 4H), 1.31 (m, 12H). ^{31}P NMR (300 MHz, CDCl₃) δ 31.5.

Scheme 20

16

24

25

26

Example 12A

24
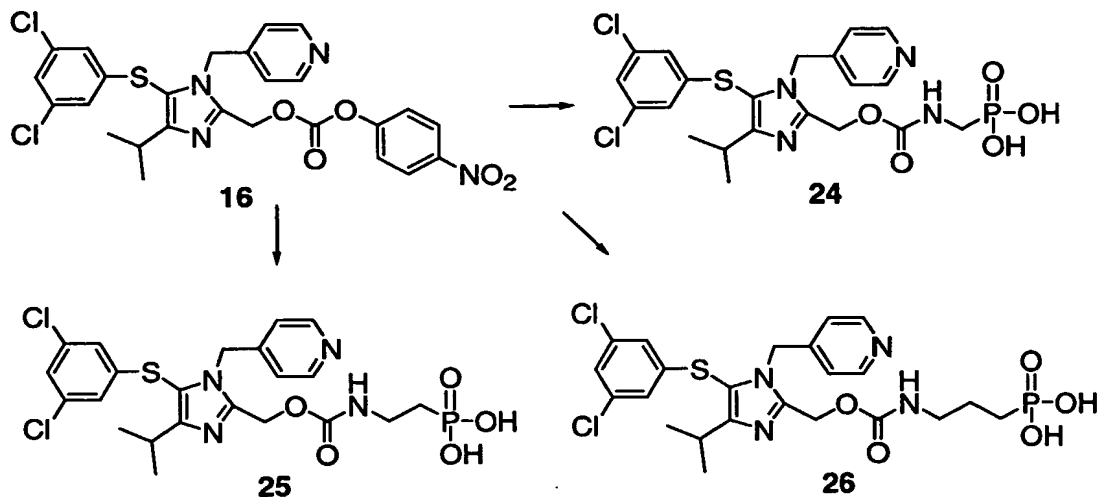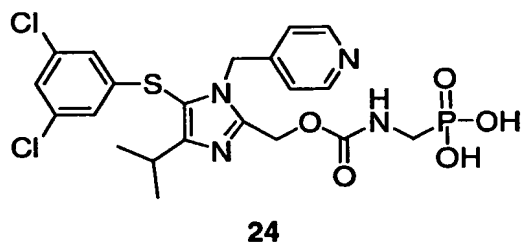
To a solution of aminomethylphosphonic acid (8 mg, 0.073 mmol) in water (1 mL) was added 1N NaOH (0.15 mL, 0.15 mmol) and carbonate **16** (21 mg, 0.037 mmol) in dioxane (1 mL). See Scheme 20. After the reaction mixture was stirred for 6 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by HPLC on C18 reverse phase chromatography (eluting 30% CH₃CN/water) to give a mixture of phosphonic acid **24** and alcohol **15**. The mixture was further purified by preparative thin layer chromatography (eluting 7.5% MeOH/CH₂Cl₂) to give {[5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonyl amino]-methyl}-phosphonic acid **24** (8 mg, 40%) as a colorless solid. ^{1}H NMR (300 MHz,

CD$_3$OD) δ 8.33 (bs, 2H), 7.10 (t, 1H), 7.04 (bs, (2H), 6.72 (d, 2H), 5.44 (s, 2H), 5.25 (s, 2H), 3.24 (m, 2H), 3.17 (m, 1H), 1.28 (d, 6H).

Example 12B
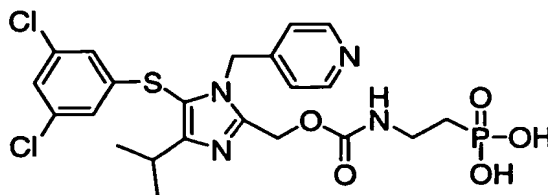
25

To a solution of 2-aminoethylphosphonic acid (12 mg, 0.098 mmol) in water (1 mL) was added 1N NaOH (0.2 mL, 0.20 mmol) and carbonate **16** (28 mg, 0.049 mmol) in dioxane (1 mL). See Scheme 20. After the reaction mixture was stirred for 6 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by HPLC on C18 reverse phase chromatography (eluting 30% CH$_3$CN/water) to give a mixture of phosphonic acid **25** and alcohol **15**. The mixture was further purified by preparative thin layer chromatography (eluting 7.5% MeOH/CH$_2$Cl$_2$) to give {2-[5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonylamino]-ethyl}-phosphonic acid **25** (13 mg, 47%) as a colorless solid. ^{1}H NMR (300 MHz, CD$_3$OD) δ 8.32 (d, 2H), 7.11 (s, 1H), 7.02 (d, 2H), 6.72 (s, 2H), 5.42 (s, 2H), 5.23 (s, 2H), 3.30 (m, 2H), 3.17 (m, 1H), 1.71 (m, 2H), 1.28 (d, 6H). ^{31}P NMR (300 MHz, CD$_3$OD) δ 20.1.

Example 12C

26
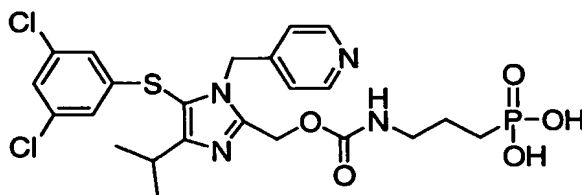
To a solution of 3-aminopropylphosphonic acid (12 mg, 0.084 mmol) in water (1 mL) was added 1N NaOH (0.17 mL, 0.17 mmol) and carbonate **16** (24 mg, 0.042 mmol) in dioxane (1 mL). See Scheme 20. After the reaction mixture was stirred for 6 h at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by HPLC on C18 reverse phase chromatography (eluting 30% CH$_3$CN/water) to give a

mixture of phosphonic acid **26** and alcohol **15**. The mixture was further purified by preparative thin layer chromatography (eluting 7.5% MeOH/CH$_2$Cl$_2$) to give {3-[5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonylamino]-propyl}-phosphonic acid **26** (11 mg, 46%) as a colorless solid. ^{1}H NMR (300 MHz, CD$_3$OD) δ 8.34 (bs, 2H), 7.11 (s, 1H), 7.02 (bs, 2H), 6.73 (d, 2H), 5.43 (s, 2H), 5.23 (s, 2H), 3.32 (m, 1H), 3.06 (bs, 2H), 1.69 (bs, 2H), 1.50 (bs, 2H), 1.28 (d, 6H).

Scheme 21
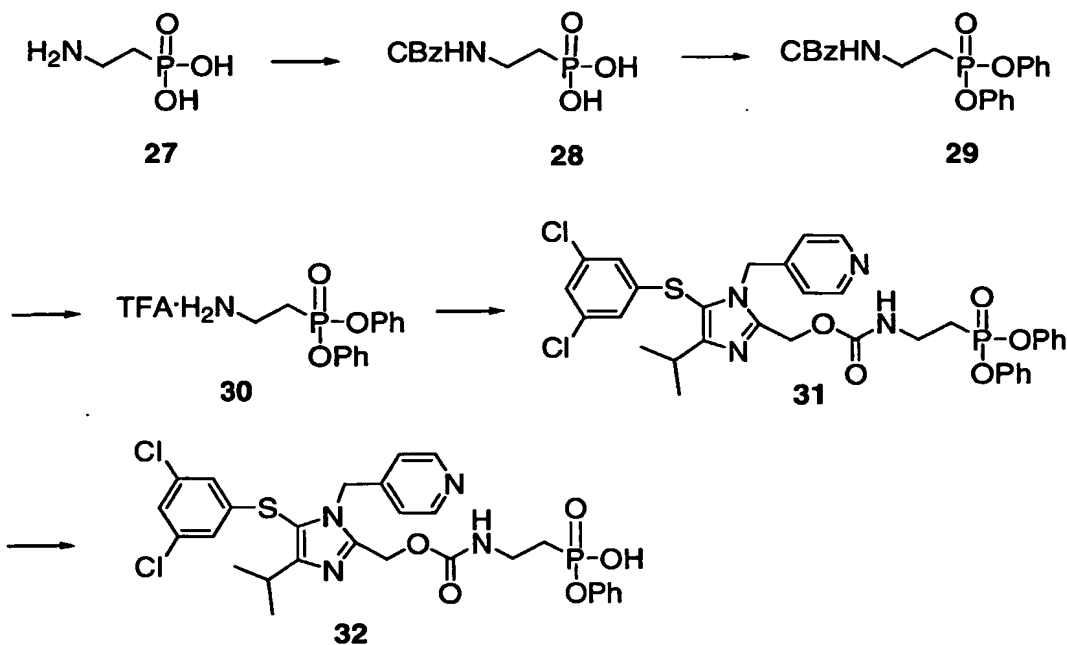
Example 13
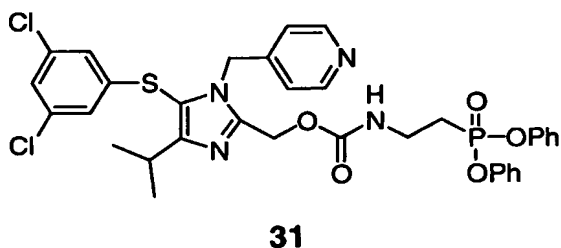
31

To a solution of 2-aminoethylphosphonic acid (1.26 g, 10.1 mmol) in 2N NaOH (10.1 mL, 20.2 mmol) was added benzyl chloroformate (1.7 mL, 12.1 mmol). See Scheme 21. After the reaction mixture was stirred for 2 d at room temperature, the mixture was partitioned between Et$_2$O and water. The aqueous phase was acidified with 6N HCl until pH = 2. The resulting colorless solid was dissolved in MeOH (75 mL) and treated with Dowex

50WX8-200 (7 g). After the mixture was stirred for 30 minutes, it was filtered and evaporated under reduced pressure to give carbamate **28** (2.37 g, 91%) as a colorless solid.

To a solution of carbamate **28** (2.35 g, 9.1 mmol) in pyridine (40 mL) was added phenol (8.53 g, 90.6 mmol) and 1,3-dicyclohexylcarbodiimide (7.47 g, 36.2 mmol). After the reaction mixture was warmed to 70°C and stirred for 5 h, the mixture was diluted with CH_3CN and filtered. The filtrate was concentrated under reduced pressure and diluted with EtOAc. The organic phase was washed with sat. NH_4Cl, sat. $NaHCO_3$, and brine, then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel twice (eluting 40-60% EtOAc/hexane) to give phosphonate **29** (2.13 g, 57%) as a colorless solid.

To a solution of phosphonate **29** (262 mg, 0.637 mmol) in isopropanol (iPrOH) (5 mL) was added TFA (0.05 mL, 0.637 mmol) and 10% Pd/C (26 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for 1 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give amine **30** (249 mg, 100%) as a colorless oil.

To a solution of carbonate **16** (40 mg, 0.070 mmol) and amine **30** (82 mg, 0.21 mmol) in CH_3CN (5 mL) was added diisopropylethylamine (0.05 mL, 0.28 mmol). After the reaction mixture was stirred for 2 h at room temperature, the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel (eluting 3-4% $MeOH/CH_2Cl_2$) to give {2-[5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-ylmethyl-1H-imidazol-2-ylmethoxycarbonylamino]-ethyl}-phosphonic acid diphenyl ester **31** (36 mg, 72%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, 2H), 7.22 (m, 4H), 7.14 (m, 2H), 7.10 (m, 2H), 6.99 (t, 1H), 6.72 (d, 2H), 6.62 (d, 2H), 5.30 (bt, 1H), 5.18 (s, 2H), 5.13 (s, 2H), 3.50 (m, 2H), 3.12 (m, 1H), 2.21 (m, 2H), 1.26 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 22.4.

Example 14
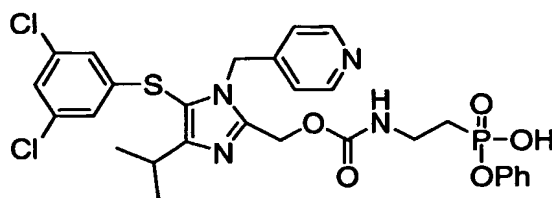
32

5

    To a solution of phosphonate **31** (11 mg, 0.015 mmol) in CH$_3$CN (0.5 mL) was added

1N LiOH (46 μL, 0.046 mmol) at 0°C. See Scheme 21. After the reaction mixture was

stirred for 2 h at 0°C, Dowex 50WX8-200 (26 mg) was added and stirring was continued for

an additional 30 min. The reaction mixture was filtered, rinsed with CH$_3$CN, and concentrated

10   under reduced pressure to give {2-[5-(3,5-dichloro-phenylsulfanyl)-4-isopropyl-1-pyridin-4-

ylmethyl-1H-imidazol-2-ylmethoxycarbonylamino]-ethyl}-phosphonic acid monophenyl ester

32 (10 mg, 100%) as a colorless oil. ^{1}H NMR (300 MHz, CD$_3$OD) δ 8.52 (d, 2H), 7.28 (m,

6H), 6.79 (m, 4H), 5.60 (s, 2H), 5.29 (s, 2H), 3.29 (m, 3H), 1.83 (m, 2H), 1.31 (d, 6H). ^{31}P

NMR (300 MHz, CD$_3$OD) δ 20.2.

Scheme 22

Example 15

36
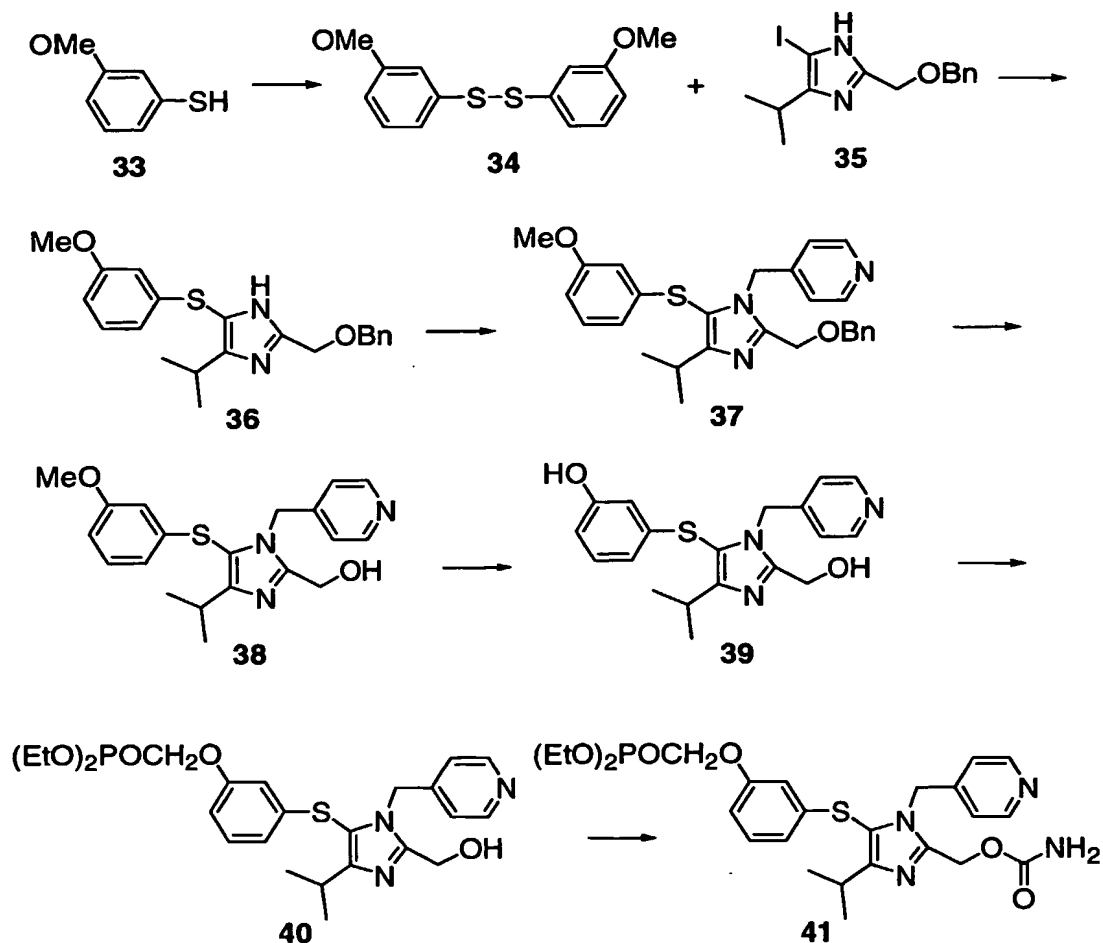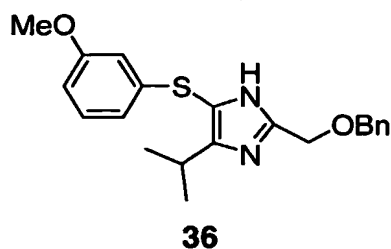
To a solution of 3-methoxybenzenethiol (0.88 mL, 7.13 mmol) in CH$_3$CN (15 mL) was added sodium iodide (214 mg, 1.43 mmol) and ferric chloride (232 mg, 1.43 mmol). See Scheme 22. After the reaction mixture was warmed to 60°C and stirred for 3 d, the mixture was concentrated under reduced pressure and partitioned between CH$_2$Cl$_2$ and water. The

organic phase was dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 5-6% EtOAc/hexane) to give disulfide **34** (851 mg, 86%) as a yellow oil. To a solution of disulfide **34** (850 mg, 3.05 mmol) in DMSO (10 mL) was added iodide **35**, also denoted previously as compound **842**, (1.21 g,

5   3.39 mmol) and lithium hydride (32 mg, 4.07 mmol). After the reaction mixture was warmed to 60°C and stirred for 16 h, the mixture was partitioned between EtOAc and water. The organic phase was washed with brine, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 30-50% EtOAc/hexane) to give 2-benzyloxymethyl-4-isopropyl-5-(3-methoxy-phenylsulfanyl)-1H-

10   imidazole **36** (247 mg, 22%) as a yellow oil.

Example 16

37

15
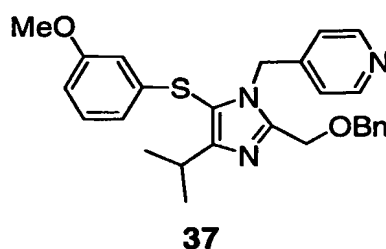
To a solution of sulfide **36** (247 mg, 0.67 mmol) in THF (10 mL) was added 4-picolylchloride (220 mg, 1.34 mmol), powder NaOH (59 mg, 1.47 mmol), lithium iodide (44 mg, 0.33 mmol), and tetrabutylammonium bromide (22 mg, 0.067 mmol). See Scheme 22. After the reaction mixture was stirred for 2 d at room temperature, the mixture was

20   partitioned between EtOAc and sat. NH₄Cl. The organic phase was dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 60-100% EtOAc/hexane) to give 4-[2-benzyloxymethyl-4-isopropyl-5-(3-methoxy-phenylsulfanyl)-imidazol-1-ylmethyl]-pyridine **37** (201 mg, 65%) as a yellow oil.

Example 17

38
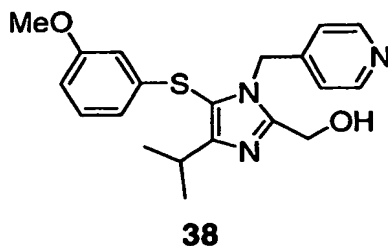
5   To a solution of amine **37** (101 mg, 0.220 mmol) in EtOH (5 mL) was added conc.

HCl (5 mL). See Scheme 22. After the reaction mixture was warmed to 80°C and stirred for

16 h, the mixture was concentrated under reduced pressure and partitioned between EtOAc

and sat. NaHCO$_3$. The organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated under

reduced pressure. The crude product was chromatographed on silica gel (eluting 5-7%

10   MeOH/CH$_2$Cl$_2$) to give [4-isopropyl-5-(3-methoxy-phenylsulfanyl)-1-pyridin-4-ylmethyl-1H-

imidazol-2-yl]-methanol **38** (71 mg, 87%) as a pale yellow oil.

Example 18

39

15
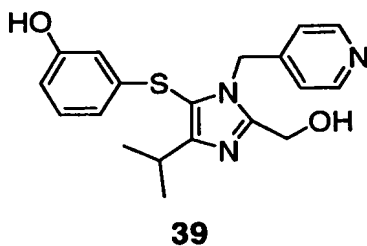
       To a solution of alcohol **38** (56 mg, 0.15 mmol) in CH$_2$Cl$_2$ (2 mL) was added 1M BBr$_3$

in CH$_2$Cl$_2$ at 0°C. See Scheme 22. After the reaction mixture was stirred for 1 h at 0°C, the

mixture was partitioned between CH$_2$Cl$_2$ and sat. NaHCO$_3$. The aqueous phase was

20   neutralized with solid NaHCO$_3$ and extracted with CH$_2$Cl$_2$ and EtOAc. The organic phase

was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product

was chromatographed on silica gel (eluting 5-10% MeOH/CH$_2$Cl$_2$) to give 3-(2-

hydroxymethyl-5-isopropyl-3-pyridin-4-ylmethyl-3H-imidazol-4-ylsulfanyl)-phenol **39** (43 mg,

81%) as a colorless solid.

25   Example 19

(EtO)₂POCH₂O
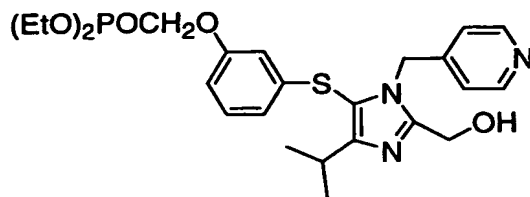
40

To a solution of phenol **39** (25 mg, 0.070 mmol) and triflate (33 mg, 0.11 mmol) in
THF (2 mL) and CH₃CN (2 mL) was added Cs₂CO₃ (46 mg, 0.14 mmol). See Scheme 22.
After the reaction mixture was stirred for 1 h at room temperature, the mixture was
partitioned between EtOAc and water. The organic phase was dried over Na₂SO₄, filtered,
and evaporated under reduced pressure. The crude product was purified by preparative thin
layer chromatography (eluting 10% MeOH/CH₂Cl₂) to give [3-(2-Hydroxymethyl-5-isopropyl-
3-pyridin-4-ylmethyl-3H-imidazol-4-ylsulfanyl)-phenoxymethyl]-phosphonic acid diethyl ester
40 (10 mg, 28%) as a colorless oil.

Example 20

(EtO)₂POCH₂O

41
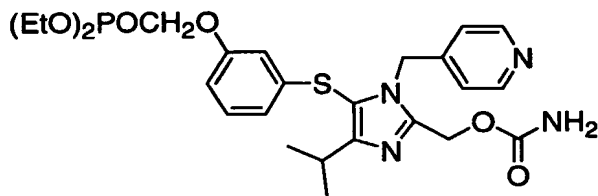
To a solution of diethylphosphonate **40** (10 mg, 0.020 mmol) in THF (2 mL) was
added trichloroacetyl isocyanate (7 μL, 0.059 mmol). See Scheme 22. After the reaction
mixture was stirred for 30 min at room temperature, the mixture was evaporated under
reduced pressure. To a solution of the concentrated residue in MeOH (2 mL) was added 1M
K₂CO₃ (0.2 mL, 0.20 mmol) at 0°C. After the reaction mixture was warmed to room
temperature and stirred for 3 h, the mixture was partitioned between EtOAc and sat. NH₄Cl.
The organic phase was dried over Na₂SO₄, filtered, and evaporated under reduced pressure.
The crude product was purified by preparative thin layer chromatography (eluting 10%
MeOH/CH₂Cl₂) to give [3-(2-hydroxymethyl-5-isopropyl-3-pyridin-4-ylmethyl-3H-imidazol-4-
ylsulfanyl)-phenoxymethyl]-phosphonic acid diethyl ester **41** (10 mg, 91%) as a colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.50 (d, 2H), 7.16 (m, 1H), 6.85 (m, 1H), 6.75 (m, 1H), 6.73 (m, 1H), 6.17 (s, 1H), 5.31 (s, 2H), 5.02 (s, 2H), 4.23 (m, 4H), 4.16 (d, 2H), 3.23 (m, 1H), 1.37 (t, 6H), 1.29 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 19.6.

Scheme 23

39   42

43

Example 21

42
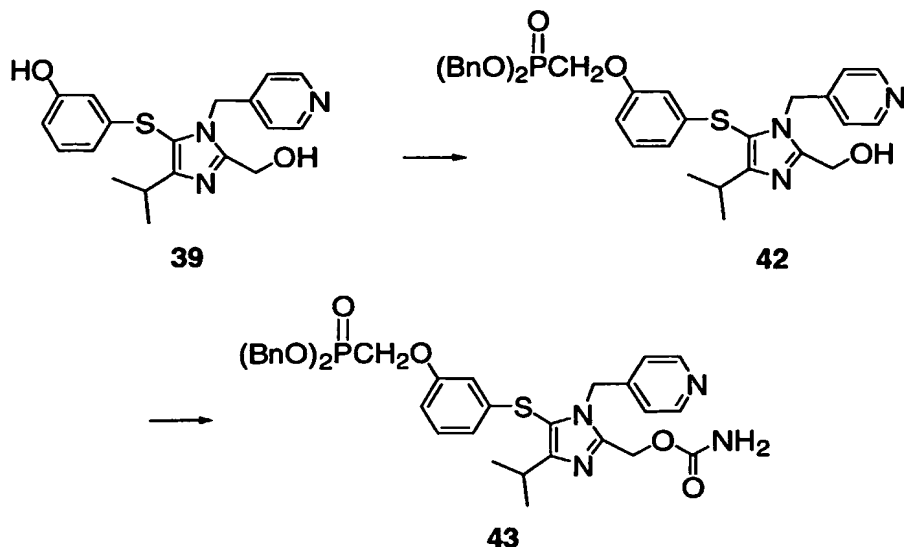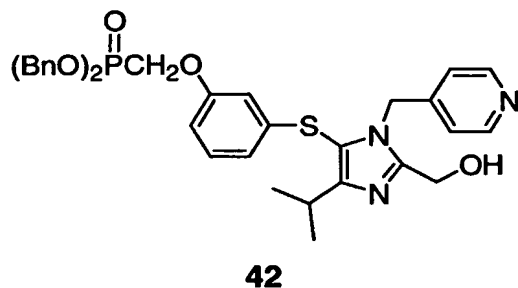
To a solution of phenol **39** (20 mg, 0.056 mmol) in THF (1 mL) and CH$_3$CN (1 mL) was added sodium hydride (60%, 5 mg, 0.112 mmol) at 0°C. See Scheme 23. After the reaction mixture was stirred for 30 min at 0°C, dibenzylphosphonyl methyltriflate (21 mg, 0.050 mmol) in THF (1 mL) was added. After the reaction mixture was stirred for 1 h at 0°C, the mixture was evaporated under reduced pressure and partitioned between EtOAc and sat. NH$_4$Cl. The organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 10% MeOH/CH$_2$Cl$_2$) to give dibenzylphosphonate **42** (5 mg, 16%) as a pale yellow oil.

Example 22

43
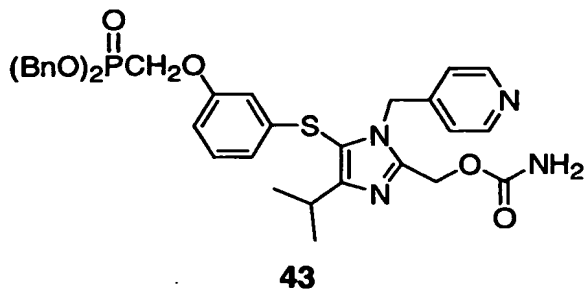
To a solution of dibenzylphosphonate **42** (5 mg, 0.0079 mmol) in CH_2Cl_2 (1 mL) was added trichloroacetyl isocyanate (5 μL, 0.049 mmol). See Scheme 23. After the reaction mixture was stirred for 15 min at room temperature, the mixture was transferred on to a 2-inch column of neutral Al_2O_3. After the reaction mixture was soaked for 30 min, the mixture was rinsed off the column with 10% $MeOH/CH_2Cl_2$ and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 10% $MeOH/CH_2Cl_2$) to give carbamate **43** (3 mg, 56%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, 2H), 7.35 (m, 10H), 7.12 (t, 1H), 6.88 (m, 2H), 6.70 (d, 1H), 6.66 (dd, 1H), 6.10 (t, 1H), 5.29 (s, 2H), 5.13 (dd, 6H), 5.05 (s, 2H), 4.14 (d, 2H), 3.24 (m, 1H), 1.30 (d, 6H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 20.3.

Preparation of phosphorus compound **874** was displayed in Scheme 24. Starting with imidazole **842**, Ar1 and Ar2 were introduced following the procedure described in US Patent No. 5326780. Benzyl group was then removed and converted to phosphorus analog **874** using the procedure described previously.

Scheme 24

842   873   874
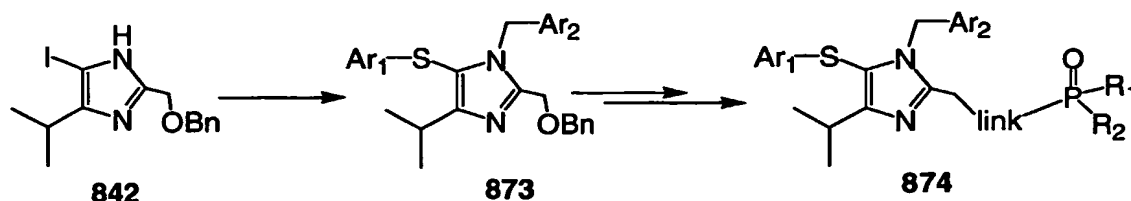
5   Scheme 25 describes preparation of compound **880**. Compound **875** was synthesized

from compound **842** using the procedures described in US Patent No. 5326780. Treatment of

875 with HCl removed the benzyl group to give alcohol **876**, which was then introduced

phenyl group with substitution of Y. Y is a function which can be converted to alcohol,

aldehyde or amine, for example -NO$_2$, -COOMe, N$_3$, and etc. Conversion of Y to the amine or

10   alcohol gave compound **878** and/or **879**, which were then used as attachment site of

phosphorus to afford phosphorus compound **880**. Hydroxyl group in compound **880** was then

converted to the desired side chain including but not limit to carbamate **881**, urea **882**,

substituted amine **883**.

Scheme 25

5
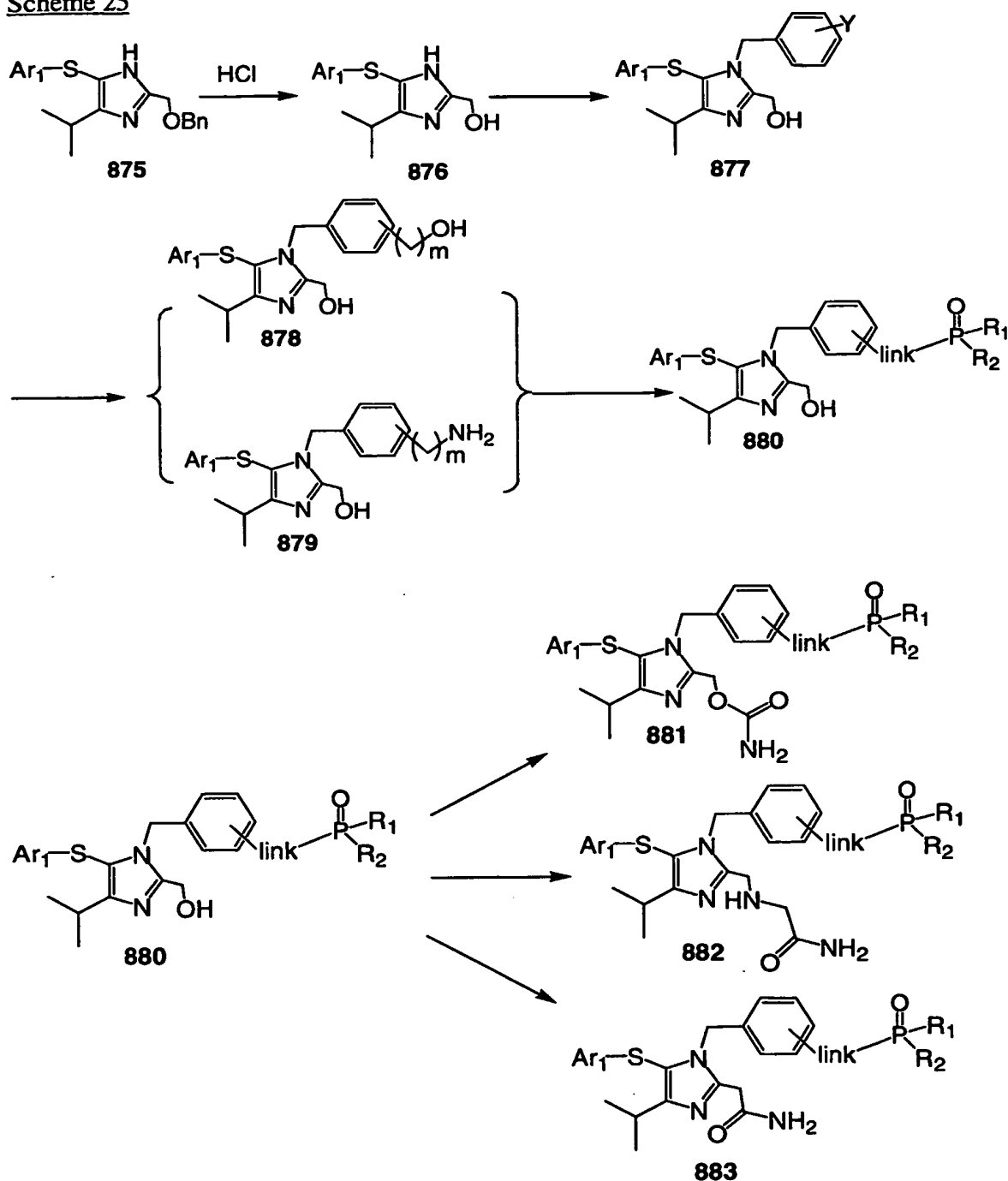
Preparation of phosphorus compound **887** is shown in Scheme 26. Compound **877** was converted to amine **884** and/or aldehyde **885**, which then reacted with aldehyde and/or amine respectively to provide phosphorus compound **886**. Treatment of compound **886** with Cl₃CCONCO provide the carbamate **887**.

10

Scheme 26

Example 22

48
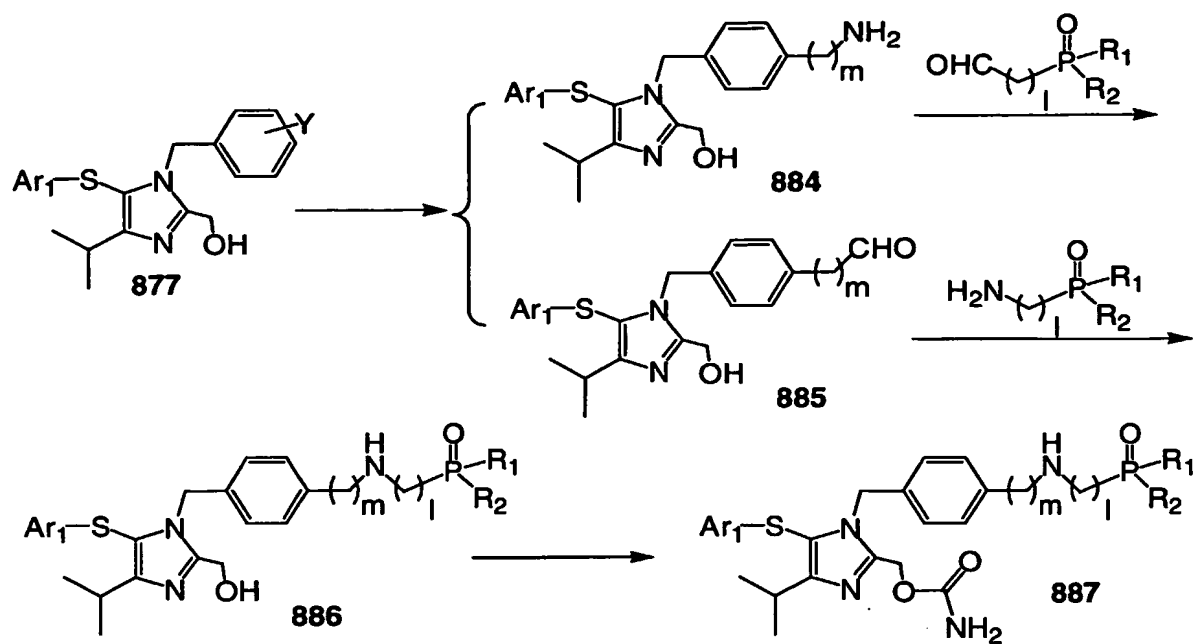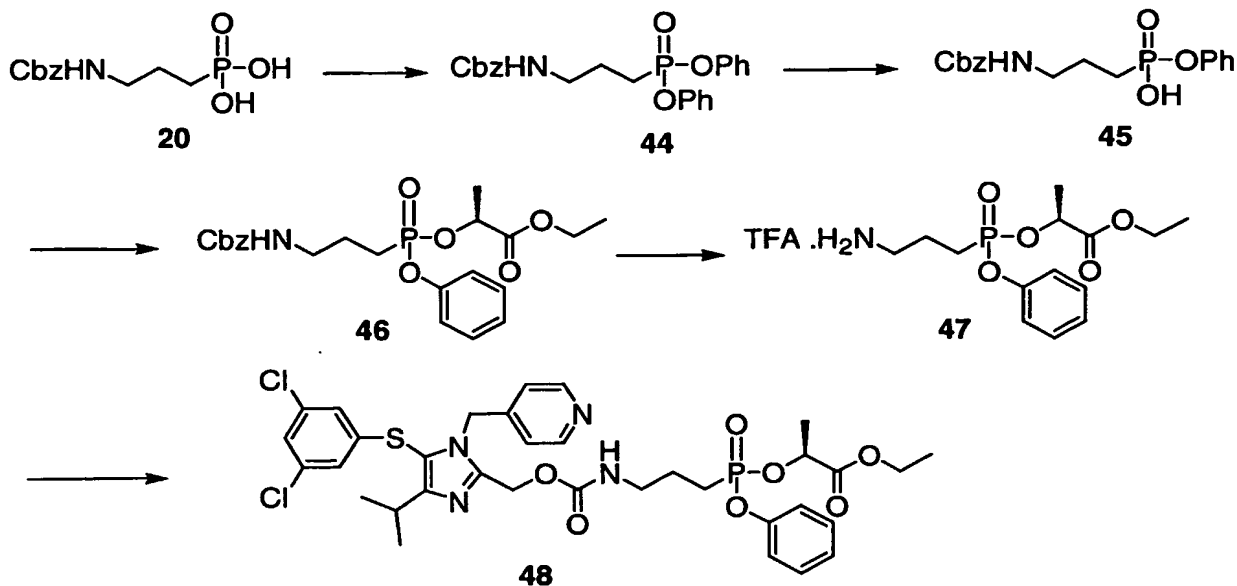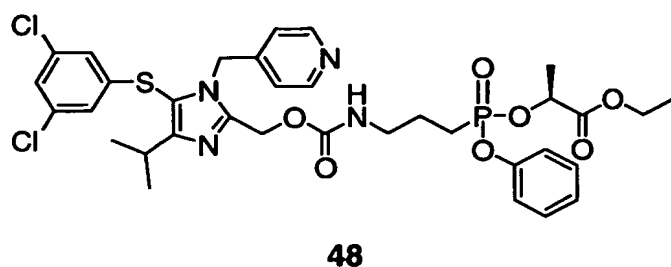
Compound **44** was prepared following the sequence of steps described in Example 13, by substituting compound **20** for compound **28**. Purification of the crude product on silica gel eluted with 3-4% MeOH/CH₂Cl₂ provided 37 mg of **48**, the title compound. ¹H NMR (500 MHz, CDCl₃) (1.3:1 diastereomeric ratio) δ 8.50 (bs, 2H), 7.35 (t, 2H), 7.20 (m, 3H), 7.06 (s, 1H), 6.90 (bs, 2H), 6.70 (s, 2H), 5.26 (bs, 2H), 5.21 (s, 2H), 4.97 (m, 1H), 4.22 (q, 2H), 3.24 (m, 2H), 3.19 (m, 1H), 2.05 (m, 2H), 1.92 (m, 2H), 1.37 (d, 3H), 1.33 (d, 6H), 1.28 (t, 3H). ³¹P NMR (300 MHz, CDCl₃) δ 30.0.
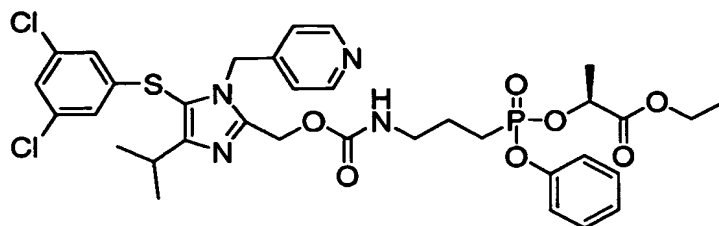
Example 23

49

The title compound **49** was prepared following the sequence of steps described in

Example 22, except for using scalmeric mixture **46** (around 13:1 ratio). Purification of the

crude final product on silica gel eluted with 3-4% MeOH/CH$_2$Cl$_2$ provided 40 mg of the title

compound. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.44 (bd, 2H), 7.32 (m, 2H), 7.19 (m, 3H), 7.04

(d, 1H), 6.80 (bs, 2H), 6.68 (m, 2H), 5.27 (d, 2H), 5.19 (d, 2H), 4.96 (m, 1H), 4.15 (m, 2H),

3.18 (m, 3H), 1.93 (m, 4H), 1.55 (d, 1.5H), 1.34 (d, 1.5H), 1.31 (d, 6H), 1.21 (m, 3H). ^{31}P

NMR (300 MHz, CDCl$_3$) δ 30.0, 28.3.

Example 24

51
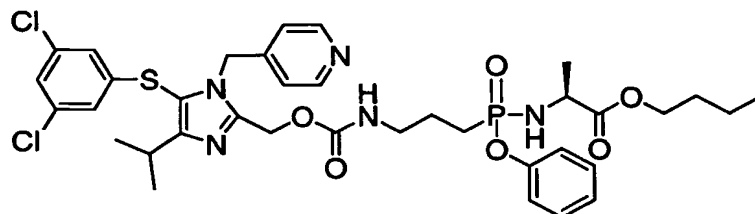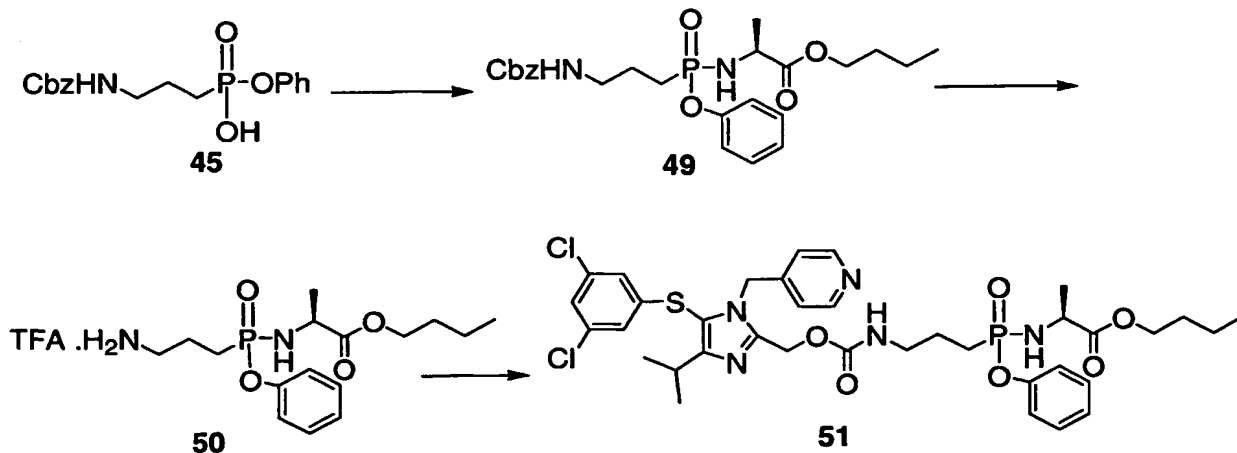
Amidate **49**: A solution of phosphonic acid **45** (66 mg, 0.19 mmol) in CH$_3$CN (5 mL)

was treated with thionyl chloride (42 μL, 0.57 mmol). After the reaction mixture was warmed

to 70°C and stirred for 2 h, the mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL) and cooled to 0°C. Triethylamine (0.11 mL, 0.76 mmol) and L-alanine n-butyl ester (104 mg, 0.57 mmol) were added. After stirring for 1 h at 0°C and 1 h at room temperature, the reaction mixture was neutralized with sat. NH_4Cl and

5   extracted with CH_2Cl_2 and EtOAc. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 60-80% EtOAc/hexane) to give amidate **49** (35 mg, 39%) as a colorless oil.

        Amine **50**: A mixture of benzyl carbamate **49** (35 mg, 0.073 mmol), trifluoroacetic acid (8 μL, 0.11 mmol) and 10% Pd/C (7 mg) in isopropyl alcohol (2 mL) was stirred under H_2

10   atmosphere (balloon) for 1 h. The mixture was then filtered through Celite. The filtrate was evaporated under reduced pressure to give amine **50** (33 mg, 99%) as a colorless oil.

        Title compound **51**: A solution of 4-nitrophenylcarbonate **16** (35 mg, 0.061 mmol) in CH_3CN (2 mL) was treated with amine **50** (33 mg, 0.072 mmol) and iPr_2NEt (21 μL, 0.122 mmol). After the reaction mixture was stirred for 1 h at room temperature, the mixture was

15   concentrated under reduced pressure. The residue was purified on silica gel (eluting 4-5% MeOH/CH_2Cl_2) to give the title compound **51** (43 mg, 91%) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.46 (bs, 2H), 7.31 (m, 2H), 7.20 (d, 2H), 7.14 (m, 1H), 7.05 (s, 1H), 6.81 (bd, 2H), 6.71 (d, 2H), 5.27 (bs, 2H), 5.19 (bs, 2H), 4.07 (m, 2H), 3.98 (m, 1H), 3.63 (m, 1H), 3.18 (m, 3H), 1.83 (m, 2H), 1.80 (m, 2H), 1.58 (m, 2H), 1.35 (m, 2H), 1.32 (d, 6H),

20   1.30 (d, 1.5H), 1.24 (d, 1.5H), 0.93 (t, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 31.6, 31.3.

<u>Example 25</u>

52
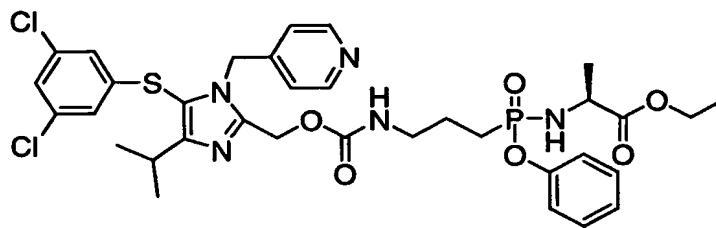
25   The title compound was prepared following the sequence of steps described in Example 24, except for substituting alanine ethyl ester for alanine n-butyl ester. Purification of the crude final product on a preparative TLC plate (5% CH_3OH/CH_2Cl_2) provided 5 mg (75%) of the title compound. ^1H NMR($CDCl_3$, 500 MHz): δ 8.46 (d, 2H), 7.32 (d, 2H), 7.20

(d, 2H), 7.15 (s, 1H), 7.05 (s, 1H), 6.82 (d, 2H), 6.70 (s, 2H), 5.27 (s, 2H), 5.19 (s, 2H), 4.12 (m, 2H), 3.70 (t, 2H), 3.19 (m, 2H), 3.12 (t, 2H), 1.48 (m, 3H), 1.47 (t, 3H), 1.25 (d,6H).

Example 26

57

53   **54**   **55**

56   **57**
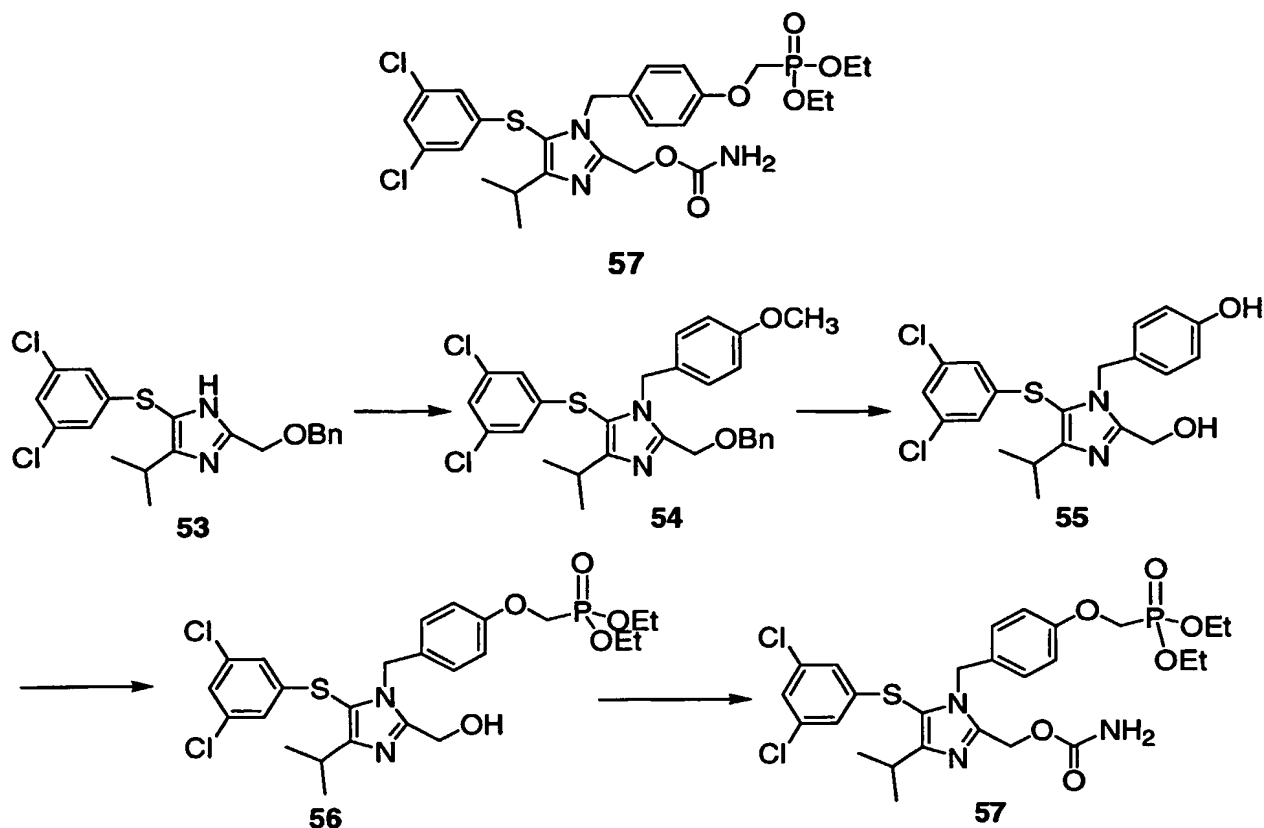
Imidazole **54**: A solution of imidazole **53** (267 mg, 0.655 mmol) in THF (10 mL) was treated with 4-methoxybenzyl chloride (0.18 mL, 1.31 mmol), powder NaOH (105 mg, 2.62 mmol), lithium iodide (88 mg, 0.655 mmol), and tetrabutylammonium bromide (105 mg, 0.327 mmol). After stirring for 4 days at room temperature, the resulting mixture was partitioned between EtOAc and sat. NH4Cl. The organic phase was dried over Na2SO4, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 20-40% EtOAc/hexane) to give imidazole **54** (289 mg, 84%) as a colorless oil.

Phenol **55**: A solution of benzyl ether **54** (151 mg, 0.286 mmol) in EtOH (5 mL) was treated with conc. HCl (5 mL). After the reaction mixture was warmed to 80°C and stirred for 2 d, the mixture was concentrated under reduced pressure and partitioned between EtOAc and sat. aqueous NaHCO3. The organic phase was dried over Na2SO4, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 60-70% EtOAc/hexane) to give the alcohol (99 mg, 79%) as a colorless solid. A solution of the

alcohol (77 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) was added 1M BBr_3 in CH_2Cl_2 (0.90 mL, 0.90 mmol) at 0°C. After the reaction mixture was stirred for 1 h at 0°C, the mixture was neutralized with sat. $NaHCO_3$ and extracted with CH_2Cl_2 and EtOAc. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was

5   chromatographed on silica gel (eluting 4-5% MeOH/CH_2Cl_2) to give phenol **55** (68 mg, 89%) as a colorless solid.

Diethylphosphonate **56**: To a solution of phenol **55** (21 mg, 0.050 mmol) in CH_3CN (1 mL) and THF (1 mL) was added trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester (18 mg, 0.060 mmol) in CH_3CN (1 mL). After the addition of Cs_2CO_3 (20 mg, 0.060

10   mmol), the reaction mixture was stirred for 2 h at room temperature. Additional triflate (18 mg, 0.060 mmol) and Cs_2CO_3 (20 mg, 0.060 mmol) were introduced. After the reaction mixture was stirred for another 2 h at room temperature, the mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and sat. NH_4Cl. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude

15   product was purified by preparative thin layer chromatography (eluting 5% MeOH/CH_2Cl_2) to give diethylphosphonate **56** (26 mg, 91%) as a pale yellow oil.

Title compound carbamate **57**: A solution of diethylphosphonate **56** (26 mg, 0.045 mmol) in CH_2Cl_2 (2 mL) was treated with trichloroacetyl isocyanate (27 µL, 0.23 mmol). After the reaction mixture was stirred for 10 min at room temperature, the mixture was concentrated

20   under reduced pressure. The residue was transferred to an Al_2O_3 column in 10% MeOH/CH_2Cl_2. After soaking on the column for 30 min, the crude product was flushed out with 10% MeOH/CH_2Cl_2 and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography eluted with 5% MeOH/CH_2Cl_2 to give title compound carbamate **57** (22 mg, 79%) as a pale yellow oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ

25   7.00 (s, 1H), 6.88 (d, 2H), 6.76 (d, 2H), 6.62 (s, 2H), 5.24 (s, 2H), 5.18 (s, 2H), 4.26 (q, 4H), 4.21 (d, 2H), 3.15 (m, 1H), 1.38 (t, 6H), 1.29 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 19.1.
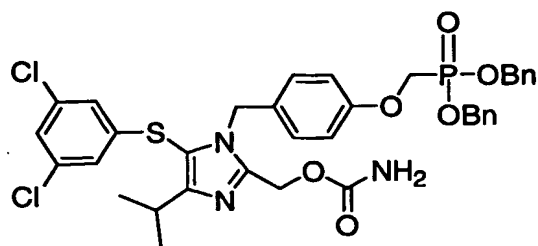
Example 27

58

The title compound **58** was prepared following the sequence of steps described in

Example 27 with substitution of trifluoro-methanesulfonic acid bis-benzyloxy-

phosphorylmethyl ester for trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester.

Purification of the crude final product on silica gel eluted with 3-4% MeOH/CH$_2$Cl$_2$ provided

33 mg of the title compound. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37 (m, 10H), 6.96 (s, 1H), 6.85

(d, 2H), 6.70 (d, 2H), 6.62 (s, 2H), 5.23 (s, 2H), 5.17 (s, 2H), 5.13 (m, 4H), 4.18 (d, 2H),

3.16 (m, 1H), 1.30 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 20.1.

Example 28

59
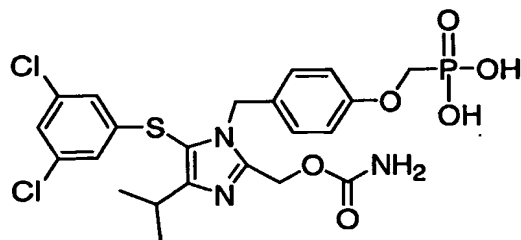
A solution of dibenzylphosphonate **58** (15 mg, 0.020 mmol) was treated 4M HCl in

dioxane (1 mL). After the reaction mixture was stirred for 18 h at room temperature, the

mixture was concentrated under reduced pressure. The crude product was purified on a C-18

column (eluting 30-40% CH$_3$CN/H$_2$O) to give phosphonic acid **59** (8 mg, 71%) as a colorless

oil. ^{1}H NMR (300 MHz, CD$_3$OD) δ 7.19 (s, 1H), 7.08 (d, 2H), 6.81 (d, 2H), 6.69 (s, 2H),

5.48 (s, 2H), 5.44 (s, 2H), 4.12 (d, 2H), 3.32 (m, 1H), 1.33 (d, 6H). ^{31}P NMR (300 MHz,

CD$_3$OD) δ 17.1.

Example 29
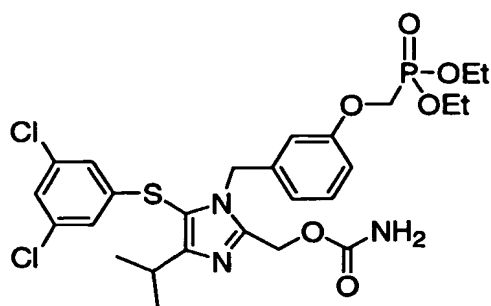
60

The title compound **60** was prepared following the sequence of steps described in Example 25, except for substituting *3*-methoxy benzyl chloride for *4*-methoxyl benzyl chloride. Purification of the crude final product on preparative thin layer chromatography eluted with 5% MeOH/CH$_2$Cl$_2$ provided 28 mg of the title compound. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.12 (t, 1H), 7.03 (s, 1H), 6.75 (d, 1H), 6.66 (s, 2H), 6.60 (d, 1H), 6.55 (s, 1H), 5.24 (s, 2H), 5.19 (s, 2H), 4.22 (q, 4H), 4.20 (d, 2H), 3.17 (m, 1H), 1.37 (t, 6H), 1.31 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 19.2.

Example 30

61

The title compound **61** was prepared following the sequence of steps described in Example 26, except for substituting *3*-methoxy benzyl chloride for *4*-methoxyl benzyl chloride. Purification of the crude final product on silica gel eluted with 3-4% MeOH/CH$_2$Cl$_2$ provided 36 mg of the title compound. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36 (m, 10H), 7.10 (t, 1H), 7.00 (s, 1H), 6.68 (d, 1H), 6.64 (s, 2H), 6.59 (d, 1H), 6.53 (s, 1H), 5.23 (s, 2H), 5.17 (s, 2H), 5.11 (m, 4H), 4.18 (d, 2H), 3.16 (m, 1H), 1.31 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 20.2.

Example 31

62
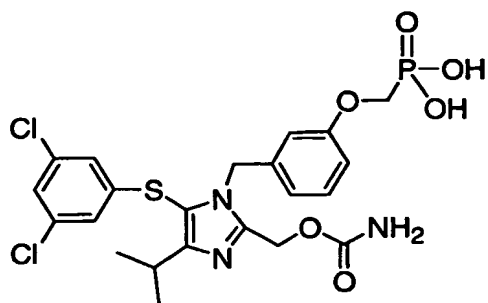
The title compound **62** was prepared following the sequence of steps described in Example 29, except for substituting compound **61** for compound **58**. Purification of the crude final product with HPLC (eluting 30-40% CH_3CN/H_2O) provided 7 mg of the title compound. ^{1}H NMR (300 MHz, CD_3OD) δ 7.18 (s, 1H), 7.13 (t, 1H), 6.81 (d, 1H), 6.77 (s, 2H), 6.72 (s, 1H), 6.68 (d, 1H), 5.49 (s, 2H), 5.37 (s, 2H), 4.12 (d, 2H), 3.33 (m, 1H), 1.34 (d, 6H). ^{31}P NMR (300 MHz, CD_3OD) δ 17.0.

Example 32
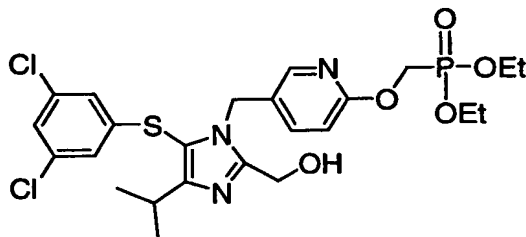
68
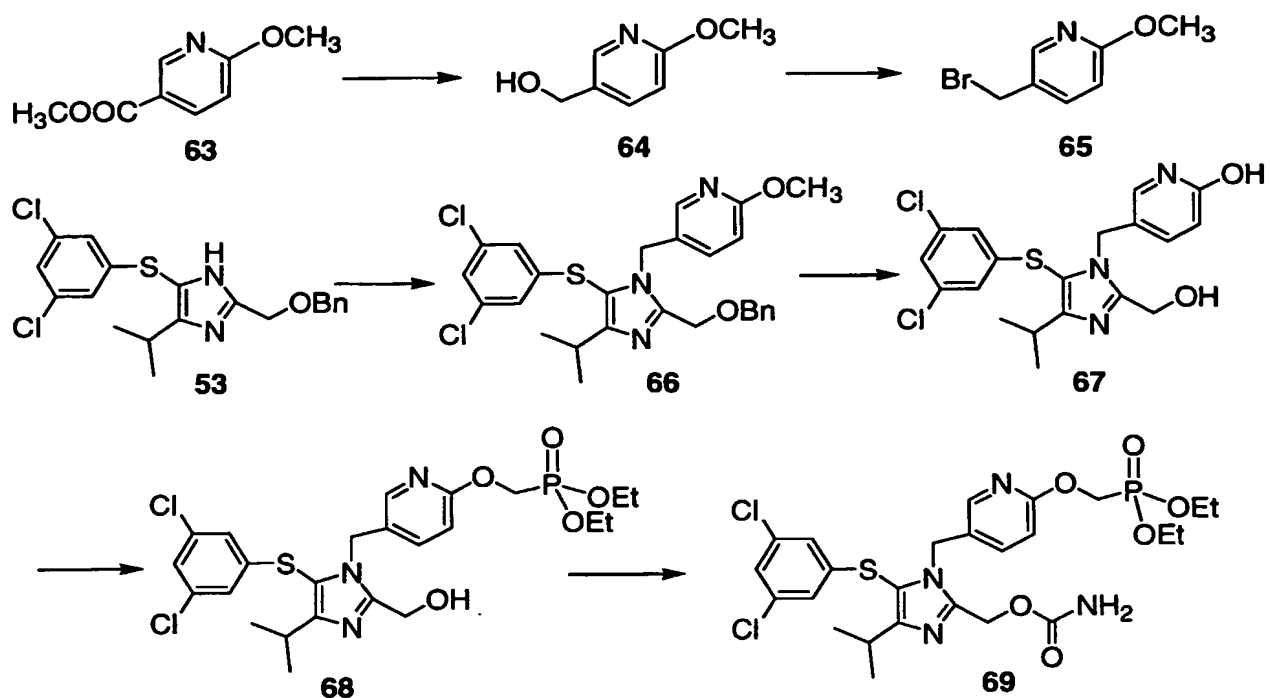
Alcohol **64**: A solution of methyl 6-methoxynicotinate **63** (2.0 g, 12 mmol) in Et₂O (50

5   mL) was treated with 1.5M DIBAL-H in toluene (16.8 mL, 25.1 mmol) at 0°C. After the

reaction mixture was stirred for 1 h at 0°C, the mixture was quenched with 1M sodium

potassium tartrate and stirred for an additional 2 h. The aqueous phase was extracted with

Et₂O and concentrated to give alcohol **64** (1.54 g, 92%) as a pale yellow oil.

Bromide **65**: A solution of alcohol **64** (700 mg, 5.0 mmol) in CH₂Cl₂ (50 mL) was treated with

10 carbon tetrabromide (2.49 g, 7.5 mmol) and triphenylphosphine (1.44 g, 5.5 mmol) at 0°C.

After the reaction mixture was stirred for 30 min at room temperature, the mixture was

partitioned between CH₂Cl₂ and sat. aqueous NaHCO₃. The organic phase was dried over

Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was purified on

silica gel (eluting 5-10% MeOH/CH₂Cl₂) to give bromide **65** (754 mg, 75%) as colorless

15 crystals.

Imidazole **66**: A solution of imidazole **53** (760 mg, 1.86 mmol) and bromide **65** (752

mg, 3.72 mmol) in THF (10 mL) was treated with powder NaOH (298 mg, 7.44 mmol),

lithium iodide (249 mg, 1.86 mmol), and tetrabutylammonium bromide (300 mg, 0.93 mmol).

After stirring for 14 h at room temperature, the mixture was partitioned between EtOAc and

20 sat. NH₄Cl. The organic phase was dried over Na₂SO₄, filtered, and evaporated under

reduced pressure. The crude product was purified on silica gel (eluting 20-30%

EtOAc/hexane) to give imidazole **66** (818 mg, 83%) as a pale yellow oil.

Diol **67**: A solution of benzyl ether **66** (348 mg, 0.658 mmol) in EtOH (3 mL) was treated
with conc. HCl (3 mL). After the reaction mixture was warmed to 80°C and stirred for 18 h,
the mixture was concentrated under reduced pressure. The crude product was
chromatographed on silica gel (eluting 5-10% MeOH/CH$_2$Cl$_2$) to give diol **67** (275 mg, 98%)
as a colorless solid.

Title compound diethylphosphonate **68**: A solution of diol **67** (40 mg, 0.094 mmol) in
THF (1 mL) was treated with trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester
(114 mg, 0.38 mmol) in THF (1 mL). After the addition of Ag$_2$CO$_3$ (52 mg, 0.19 mmol), the
reaction mixture was stirred for 5 d at room temperature. The mixture was quenched with sat.
NaHCO$_3$ and sat. NaCl, and extracted with EtOAc. The organic phase was dried over
Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was
chromatographed by silica gel (eluting 3-4% MeOH/CH$_2$Cl$_2$) and by preparative thin layer
chromatography (eluting 4% MeOH/CH$_2$Cl$_2$) to give the title compound diethylphosphonate
68 (23 mg, 43%) as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.92 (s, 1H), 7.39 (d, 1H),
7.00 (s, 1H), 6.65 (d, 1H), 6.55 (d, 2H), 5.20 (s, 2H), 4.81 (s, 2H), 4.55 (d, 2H), 4.21 (m,
4H), 3.08 (m, 1H), 1.35 (t, 6H), 1.20 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 20.7.

Example 33
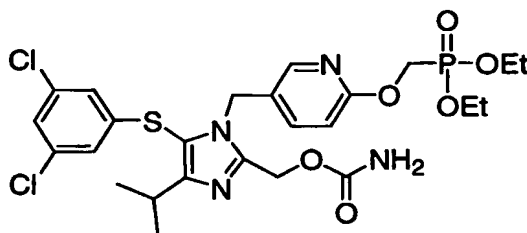
69

A solution of diethylphosphonate **68** (13 mg, 0.023 mmol) in CH$_2$Cl$_2$ (0.5 mL) was
treated with trichloroacetyl isocyanate (13 µL, 0.11 mmol). After the reaction mixture was
stirred for 10 min at room temperature, the mixture was concentrated under reduced pressure.
The residue was transferred to an Al$_2$O$_3$ column in 10% MeOH/CH$_2$Cl$_2$. After soaking on the
column for 30 min, the crude product was flushed out with 10% MeOH/CH$_2$Cl$_2$ and
concentrated under reduced pressure. The crude product was purified by preparative thin
layer chromatography (eluting 5% MeOH/CH$_2$Cl$_2$) to give carbamate **69** (13 mg, 92%) as a
pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.78 (d, 1H), 7.20 (dd, 1H), 7.03 (t, 1H), 6.65

(d, 1H), 6.62 (d, 2H), 5.24 (s, 2H), 5.16 (s, 2H), 4.74 (bs, 2H), 4.58 (d, 2H), 4.20 (m, 4H), 3.13 (m, 1H), 1.35 (t, 6H), 1.27 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 20.7.
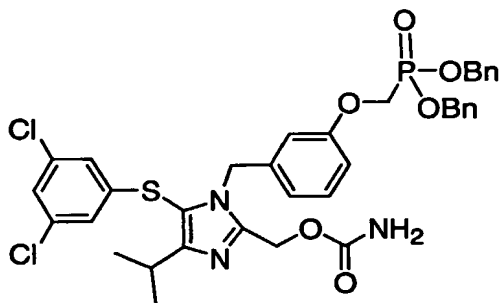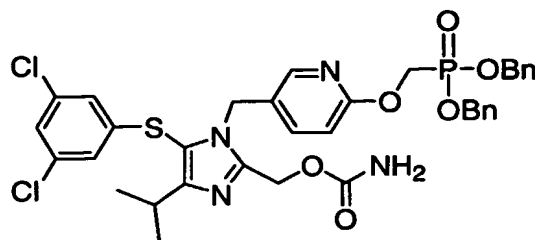
Example 34

70

The title compound **70** was prepared following the sequence of steps described in Example 32, except for substituting trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester for trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester. Purification of the crude final product on silica gel eluted with 50-60% CH$_3$CN/H$_2$O provided 12 mg of the title compound. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.78 (s, 1H), 7.34 (m, 10H), 7.19 (dd, 1H), 7.02 (t, 1H), 6.63 (s, 1H), 6.61 (d, 2H), 5.38 (s, 2H), 5.25 (s, 2H), 5.11 (m, 4H), 4.62 (d, 2H), 3.24 (m, 1H), 1.33 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 21.4.

Example 35

71

The title compound **71** was prepared following the sequence of steps described in Example 29, except for substituting compound **70** for compound **28**. Purification of the crude final product with HPLC provided 2 mg of the title compound. ^{1}H NMR (300 MHz, CD$_3$OD) δ 7.90 (s, 1H), 7.44 (d, 1H), 7.13 (t, 1H), 6.72 (m, 3H), 5.39 (s, 2H), 5.34 (s, 2H), 4.39 (d, 2H), 3.30 (m, 1H), 1.28 (d, 6H).

Example 36

- 168 -
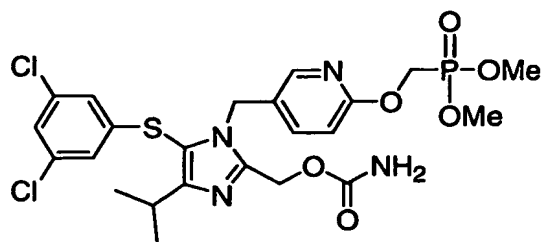
72

To a solution of phosphonic acid **72** (33 mg, 0.058 mmol) in DMF (2 mL) was added
benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (91 mg, 0.175 mmol),
iPr₂NEt (30 µL, 0.175 mmol), and MeOH (0.24 mL, 5.83 mmol). After the reaction mixture
was stirred for 2 d at room temperature, the mixture was partitioned between EtOAc and sat.
NH₄Cl. The organic phase was dried over Na₂SO₄, filtered, and evaporated under reduced
pressure. Purification of the crude final product on silica gel eluted with 3-5% MeOH/CH₂Cl₂
and by preparative thin layer chromatography (eluting 5% MeOH/CH₂Cl₂) provided 6 mg of
the title compound as a colorless solid. ¹H NMR (300 MHz, CDCl₃) δ 7.79 (d, 1H), 7.21 (dd,
1H), 7.04 (s, 1H), 6.66 (d, 1H), 6.62 (d, 2H), 5.25 (s, 2H), 5.17 (s, 2H), 4.70 (bs, 2H), 4.63
(d, 2H), 3.84 (d, 6H), 3.14 (m, 1H), 1.28 (d, 6H). ³¹P NMR (300 MHz, CDCl₃) δ 23.2.

Example 37
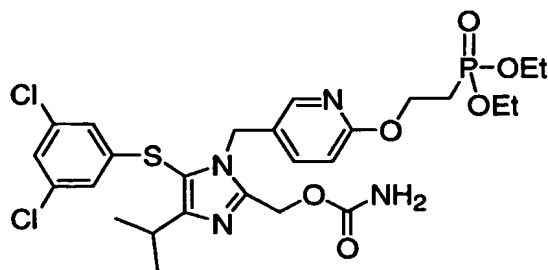
73

A solution of diol **67** (50 mg, 0.118 mmol) in CH₂Cl₂ (5 mL) was treated with diethyl
(2-bromoethyl)-phosphonate (64 µL, 0.354 mmol) and Ag₂CO₃ (65 mg, 0.236 mmol). After
the reaction mixture was stirred for 3 d at 40°C, additional phosphonate (64 µL, 0.354 mmol),
Ag₂CO₃ (65 mg, 0.236 mmol), and benzene (5 mL) were introduced. After the reaction
mixture was stirred for another 4 days at 70°C, the mixture was filtered through a medium-
fritted funnel. The crude product was chromatographed by silica gel (eluting 4-5%
MeOH/CH₂Cl₂) to give diethylphosphonate **74** (8 mg, 12%) as a colorless oil. ¹H NMR (300

MHz, CDCl$_3$) δ 7.81 (bs, 1H), 7.17 (dd, 1H), 7.03 (t, 1H), 6.60 (d, 2H), 6.52 (d, 2H), 5.25 (s, 2H), 5.15 (s, 2H), 4.71 (bs, 2H), 4.47 (m, 2H), 4.14 (m, 4H), 3.12 (m, 1H), 2.27 (m, 2H), 1.34 (t, 6H), 1.27 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 28.0.
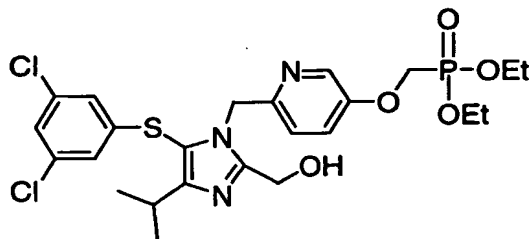
5   Example 38

74

The title compound **74** was prepared following the sequence of steps described in Example 33, except for substituting 6-bromomethyl-3-methoxy pyridine for 5-bromomethyl-2-

10   methoxy pyridine **65**. Purification of the crude final product on silica gel with 4-5% MeOH/CH$_2$Cl$_2$ provided 66 mg of the title compound. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.17 (d, 1H), 7.01 (d, 1H), 6.93 (m, 2H), 6.41 (d, 2H), 5.26 (s, 2H), 4.94 (s, 2H), 4.22 (q, 4H), 4.12 (m, 2H), 3.08 (m, 1H), 1.38 (t, 6H), 1.25 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 17.7.
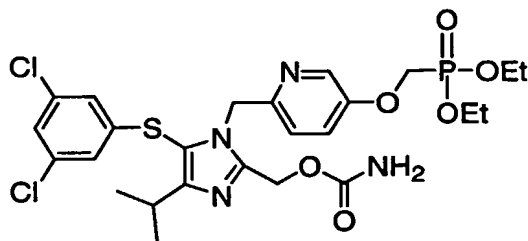
15   Example 39

75

The title compound **75** was prepared following the sequence of steps described in

20   Example 34, except for substituting compound **74** for compound **33**. Purification of the crude final product on preparative thin layer chromatography eluted with 5% MeOH/CH$_2$Cl$_2$ provided 15 mg the title compound. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.18 (d, 1H), 6.98 (m, 1H), 6.96 (m, 1H), 6.79 (d, 1H), 6.58 (d, 2H), 5.35 (s, 2H), 5.32 (s, 2H), 4.83 (bs, 2H), 4.25 (q, 4H), 4.24 (m, 2H), 3.14 (m, 1H), 1.39 (t, 6H), 1.28 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$)
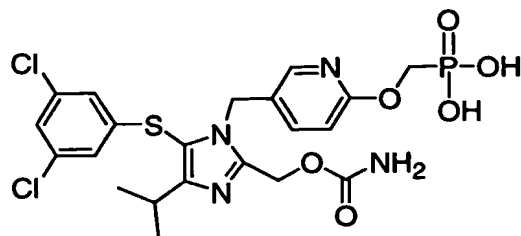
25   δ 18.1.

Example 40

76
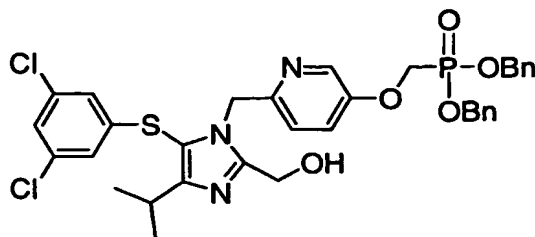
The title compound **76** was prepared following the sequence of steps described in Example 39, except for substituting trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester for trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester. Purification of the crude final product on silica gel eluted with 4% MeOH/CH$_2$Cl$_2$ provided 67 mg of the title compound. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.05 (d, 1H), 7.36 (m, 10H), 6.95 (d, 1H), 6.81 (m, 2H), 6.37 (d, 2H), 5.22 (s, 2H), 5.13 (m, 4H), 4.91 (s, 2H), 4.11 (d, 2H), 3.05 (m, 1H), 1.22 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 18.8.

Example 41

77
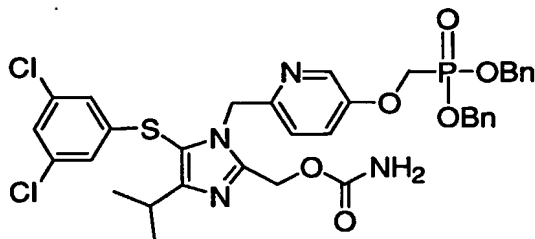
The title compound **77** was prepared following the sequence of steps described in Example 34, except for substituting compound **76** for compound **33**. Purification of the crude final product on silica gel eluted with 4-5% MeOH/CH$_2$Cl$_2$ provided 35 mg of the title compound. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.07 (d, 1H), 7.36 (m, 10H), 6.85 (m, 2H), 6.72 (d, 1H), 6.55 (d, 2H), 5.35 (s, 2H), 5.29 (s, 2H), 5.13 (m, 4H), 4.74 (bs, 2H), 4.15 (d, 2H), 3.13 (m, 1H), 1.28 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 19.2.

Example 42

78

The title compound **78** was prepared following the sequence of steps described in Example 29, except for substituting compound **77** for compound **28**. Purification of the crude final product on a C-18 column eluted with 30% CH_3CN/H_2O provided 6 mg of the title compound. ^{1}H NMR (300 MHz, CD_3OD) δ 8.16 (bs, 1H), 7.21 (bs, 2H), 7.18 (bs, 1H), 6.70 (d, 2H), 5.64 (s, 2H), 5.49 (s, 2H), 4.21 (d, 2H), 3.34 (m, 1H), 1.34 (d, 6H). ^{31}P NMR (300 MHz, CD_3OD) δ 16.0.

Example 43

81

59   **79**
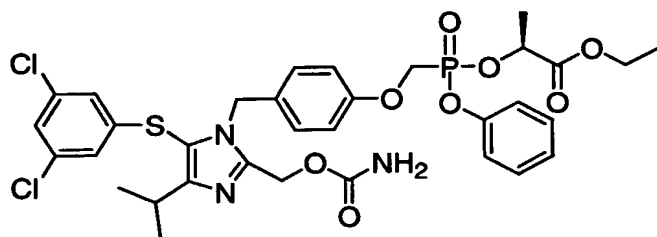
80   **81**
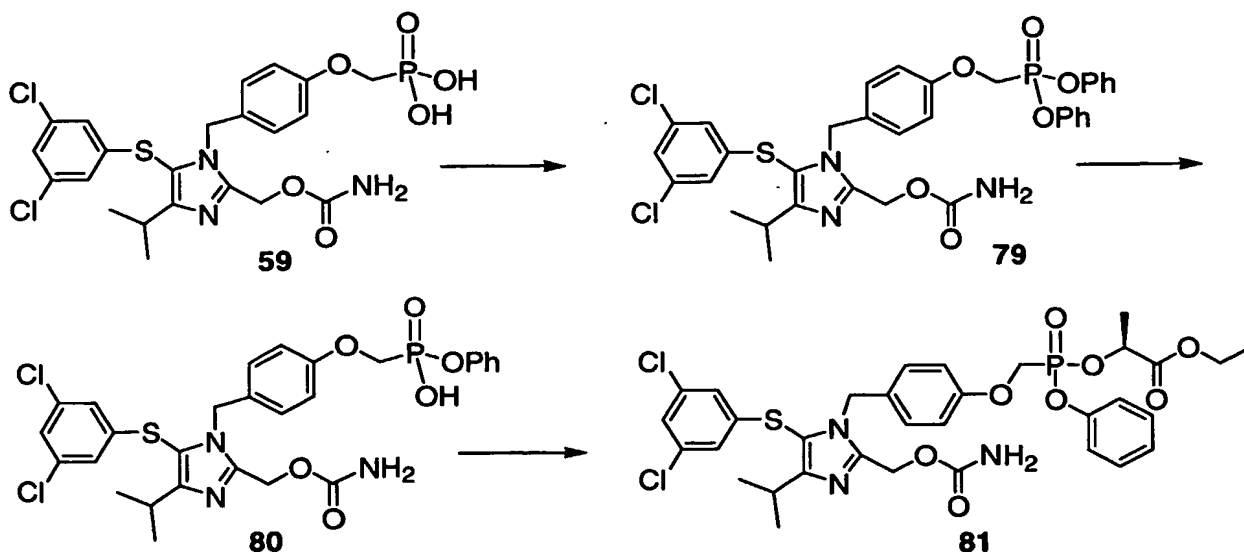
Diphenylphosphonate **79**: A solution of phosphonic acid **59** (389 mg, 0.694 mmol) in pyridine (5 mL) was treated with phenol (653 mg, 6.94 mmol) and 1,3-dicyclohexylcarbodiimide (573 mg, 2.78 mmol). After stirring at 70°C for 2 h, the mixture was diluted with CH$_3$CN and filtered through a fritted funnel. The filtrate was partitioned

5   between EtOAc and sat. NH$_4$Cl, and extracted with EtOAc. The organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 60-80% EtOAc/hexane) to give diphenylphosphonate **79** (278 mg, 56%) as a colorless oil.

Phosphonic acid **80**: A solution of diphenylphosphonate **79** (258 mg, 0.362 mmol) in

10   CH$_3$CN (20 mL) was treated with 1N NaOH (0.72 mL, 0.724 mmol) at 0°C. After the reaction mixture was stirred for 3 h at 0°C, the mixture was filtered through Dowex 50WX8-400 acidic resin (380 mg), rinsed with MeOH, and concentrated under reduced pressure to give phosphonic acid **80** (157 mg, 68%) as a colorless solid.

Title compound **81**: A solution of phosphonic acid **80** (35 mg, 0.055 mmol) in CH$_3$CN

15   (1 mL) and THF (1 mL) was treated with thionyl chloride (12 μL, 0.16 mmol). After the reaction mixture was warmed to 70°C and stirred for 2 h, the mixture was concentrated under reduced pressure. The residue was then dissolved in CH$_2$Cl$_2$ (2 mL) and cooled to 0°C. Triethylamine (31 μL, 0.22 mmol) and ethyl S-(-)-lactate (19 μL, 0.16 mmol) were added. After stirring for 1 h at 0°C and 1 h at room temperature, the reaction mixture was neutralized

20   with sat. NH$_4$Cl and extracted with CH$_2$Cl$_2$ and EtOAc. The organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 70% EtOAc/hexane) to give ethyl lactate **81** (7 mg, 17%) as a colorless solid. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.30 (m, 5H), 6.99 (d, 1H), 6.82 (m, 4H), 6.63 (d, 2H), 5.23 (s, 2H), 5.18 (s, 2H), 5.14 (m, 1H), 4.67 (bs, 2H), 4.51 (d,

25   2H), 4.20 (m, 2H), 3.16 (m, 1H), 1.61 (d, 1.5H), 1.50 (d, 1.5H), 1.30 (d, 6H), 1.24 (m, 3H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 17.0, 15.0.

Example 44
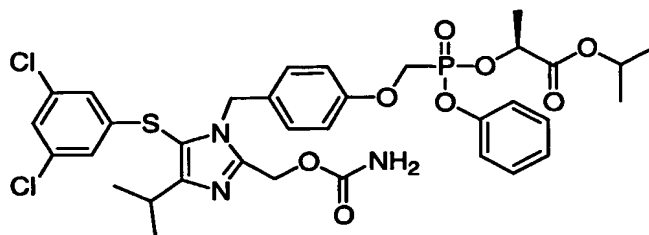
82

The title compound **82** was prepared following the sequence of steps described in Example 44, except for reacting monophosphonic acid **80** with isopropyl lactate. Purification of the crude final product on silica gel eluted with 70-90% EtOAc/hexane provided 5.4 mg of the title compound. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35 (m, 3H), 7.25 (m, 3H), 7.0 (s, 0.5H), 6.98 (s, 0.5H), 6.86 (m, 2H), 6.79 (m, 2H), 6.64 (s, 1H), 6.61 (s, 1H), 5.22 (s, 2H), 5.17 (s, 2H), 5.06 (b, 1H), 4.62 (b, 2H), 4.53 (m, 2H), 4.38 (q, 1H), 3.15 (m, 1H), 1.60 (d, 1.5H), 1.48 (d, 1.5H), 1.30 (d, 3H), 1.28 (d, 3H), 1.20 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 17.04, 14.94 (1:1 diastereomeric ratio).

Example 45
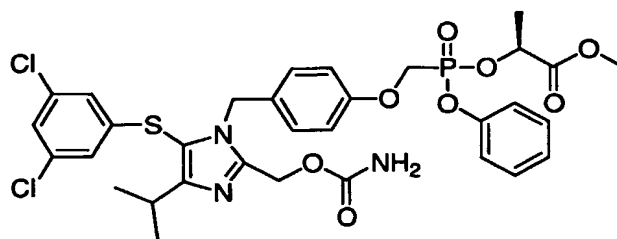
83

The title compound **83** was prepared following the sequence of steps described in Example 44, except for reacting monophosphonic acid **80** with methyl lactate. Purification of the crude final product on silica gel eluted with 70-90% EtOAc/hexane provided 2.7 mg of the title compound. ^{1}H NMR (300 MHz, CD$_3$CN) δ 7.40 (m, 2H), 7.25 (m, 3H), 7.08 (s, 1H), 6.98 (d, 2H), 6.77 (d, 2H), 6.64 (s, 2H), 5.20 (s, 2H), 5.16 (s, 2H), 5.13 (b, 1H), 4.47 (m, 2H), 3.72 (s, 2H), 3.67 (s, 1H), 3.09 (m, 1H), 1.56 (d, 1H), 1.51 (d, 2H), 1.20 (d, 6H). ^{31}P NMR (300 MHz, CD$_3$CN) δ 16.86, 15.80 (2.37:1 diastereomeric ratio).

Example 46

84

- 174 -
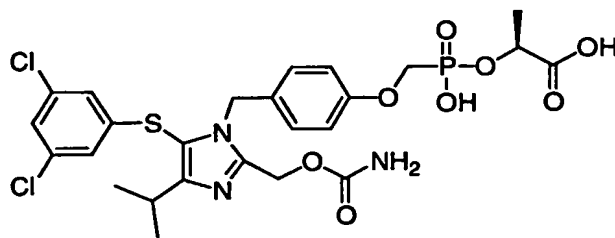
A solution of mono-lactate phosphonate compound **83** (131 mg, 0.18 mmol) in DMSO/MeCN (1 mL/2 mL) and PBS buffer (10 mL) was treated with esterase (400 µL). After the reaction mixture was warmed to 40°C and stirred for 7 days, the mixture was filtered and concentrated under reduced pressure. Purification of the crude product on C_{18} column eluted with MeCN/H$_2$O provided 17.3 mg (15 %) of the title compound **84**. ^{1}H NMR (300 MHz, CD$_3$OD) δ 7.20 (s, 1H), 7.02 (d, 2H), 6.79 (d, 2H), 6.71 (s, 2H), 5.40 (s, 2H), 5.35 (s, 2H), 5.34 (b, 1H) 4.10 (bd, 2H), 3.26 (m, 1H), 1.50 (d, 3H), 1.30 (d, 6H). ^{31}P NMR (300 MHz, CD$_3$OD) δ 14.2.
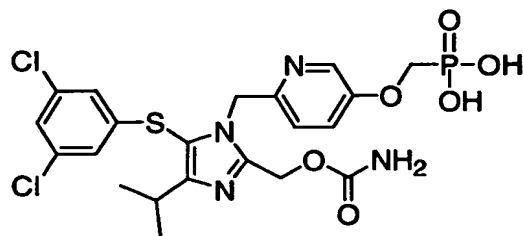
Example 47

85

The title compound **85** was prepared following the sequence of steps described in Example 44, except for reacting monophosphonic acid **80** with L-alanine ethyl ester. Purification of the crude final product on preparative thin layer chromatography eluted with 80% EtOAc/hexane provided 7 mg of the title compound. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.26 (m, 5H), 6.98 (d, 1H), 6.87 (d, 2H), 6.73 (t, 2H), 6.62 (s, 2H), 5.21 (s, 2H), 5.17 (s, 2H), 4.28 (bs, 2H), 4.25 (m, 2H), 4.10 (m, 2H), 4.02 (m, 1H), 3.66 (m, 1H), 3.14 (m, 1H), 1.28 (d, 6H), 1.24 (m, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 20.2, 19.1.
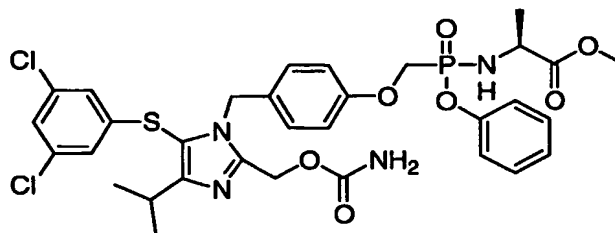
Example 48

86

The title compound **86** was prepared following the sequence of steps described in Example 44, except for reacting monophosphonic acid **80** with L-alanine methyl ester.

Purification of the crude final product on preparative thin layer chromatography eluted with 80% EtOAc/hexane provided 8 mg of the title compound. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25 (m, 5H), 6.98 (d, 1H), 6.88 (d, 2H), 6.73 (t, 2H), 6.61 (bs, 2H), 5.21 (d, 2H), 5.17 (s, 2H), 4.66 (bs, 2H), 4.25 (m, 3H), 3.66 (s, 1.5H), 3.64 (m, 1H), 3.59 (m, 1.5H), 3.14 (m, 1H), 1.36 (t, 6H), 1.28 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 20.2, 19.0.
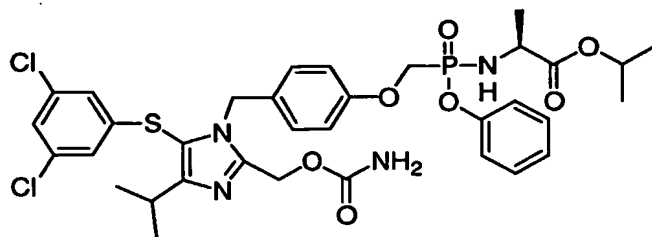
Example 49

87

The title compound **87** was prepared following the sequence of steps described in Example 44, except for reacting monophosphonic acid **80** with L-alanine isopropyl ester. Purification of the crude final product on preparative thin layer chromatography eluted with 80% EtOAc/hexane provided 7 mg of the title compound. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25 (m, 5H), 6.98 (m, 1H), 6.87 (d, 2H), 6.74 (m, 2H), 6.61 (bs, 2H), 5.22 (d, 2H), 5.18 (s, 2H), 4.93 (m, 1H), 4.68 (bs, 2H), 4.25 (m, 3H), 3.66 (s, 1H), 3.15 (m, 1H), 1.34 (m, 3H), 1.29 (d, 6H), 1.17 (m, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 20.1, 19.1.
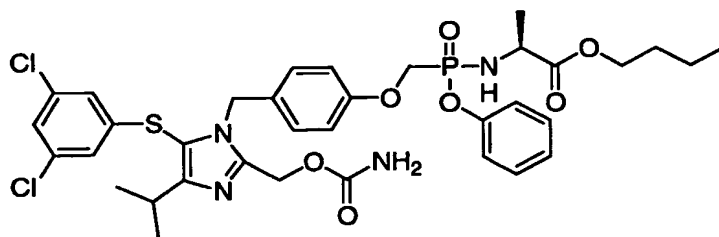
Example 50

88

The title compound **88** was prepared following the sequence of steps described in Example 44, except for reacting monophosphonic acid **80** with L-alanine *n*-butyl ester. Purification of the crude final product on preparative thin layer chromatography eluted with 80% EtOAc/hexane provided 6 mg of the title compound. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25 (m, 5H), 6.98 (bd, 1H), 6.88 (d, 2H), 6.73 (t, 2H), 6.61 (d, 2H), 5.22 (d, 2H), 5.17 (s, 2H),

4.63 (bs, 2H), 4.25 (m, 3H), 4.06 (m, 2H), 3.65 (m, 1H), 3.14 (m, 1H), 1.58 (m, 4H), 1.36 (m, 3H), 1.28 (d, 6H), 0.90 (t, 3H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 20.2, 19.1.
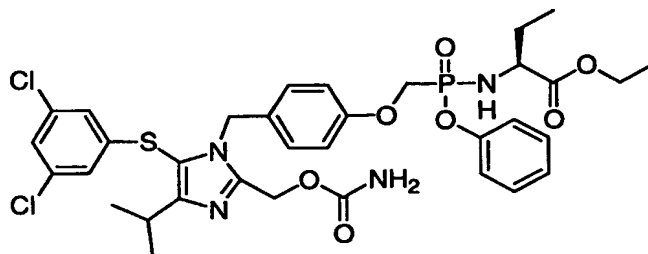
Example 51

89

The title compound **89** was prepared following the sequence of steps described in Example 44, except for reacting monophosphonic acid **80** with L-alanine *n*-butyl ester. Purification of the crude final product on preparative thin layer chromatography eluted with 80% EtOAc/hexane provided 4 mg of the title compound. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.24 (m, 5H), 6.98 (m, 1H), 6.87 (d, 2H), 6.74 (t, 2H), 6.62 (d, 2H), 5.21 (d, 2H), 5.17 (s, 2H), 4.64 (bs, 2H), 4.24 (m, 2H), 4.11 (m, 3H), 3.58 (m, 1H), 3.15 (m, 1H), 1.28 (d, 6H), 1.19 (m, 5H), 0.84 (m, 3H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 20.4, 19.4.

Example 52
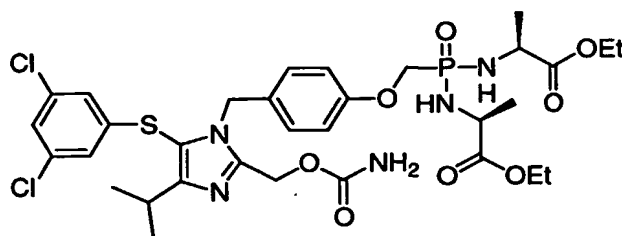
90

To a solution of phosphonic acid **59** (61 mg, 0.11 mmol) in DMF (1 mL) was added benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (169 mg, 0.32 mmol), L-alanine ethyl ester (50 mg, 0.32 mmol), and DIEA (151 µL, 0.87 mmol). The reaction mixture was stirred for 5 hours at room temperature. Then the mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with HCl (5 % aq), and extracted with EtOAc (3x). The organic phase was washed with sat. NaHCO$_3$, dried over Na$_2$SO$_4$, and evaporated under reduced pressure. The crude product was purified on silica gel eluted with 5-8% MeOH/CH$_2$Cl$_2$ to give 5.5 mg of compound bis-amidate **90** as white solid.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.06 (s, 1H), 6.88 (d, 2H), 6.73 (d, 2H), 6.62 (s, 2H), 5.23 (s, 2H), 5.17 (s, 2H), 4.70 (bs, 2H), 4.25 (bm, 8H), 3.40 (q, 2H), 3.16 (m, 1H), 1.44 (t, 6H), 1.24 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 19.41.
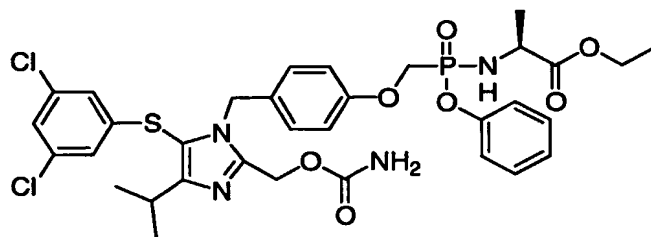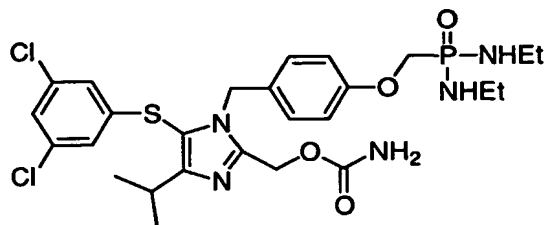
Example 53

91

The title compound **91** was prepared following the sequence of steps described in Example 52, except for substituting ethyl amine for L-alanine ethyl ester. Purification of the crude final product on silica gel eluted with 4-10% MeOH/CH$_2$Cl$_2$ provided 14.8 mg of the title compound. ^{1}H NMR (300 MHz, CD$_3$OD) δ 7.07 (s, 1H), 6.99 (d, 2H), 6.77 (d, 2H), 6.60 (s, 2H), 5.27 (s, 2H), 5.22 (s, 2H), 4.07 (d, 2H), 3.09 (m, 1H), 3.01 (bm, 4H), 1.24 (d, 6H), 1.16 (t, 6H). ^{31}P NMR (300 MHz, CD$_3$OD) δ 24.66.

Example 54
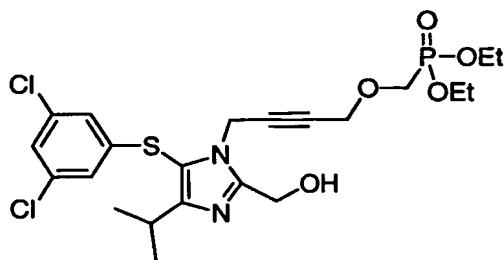
97
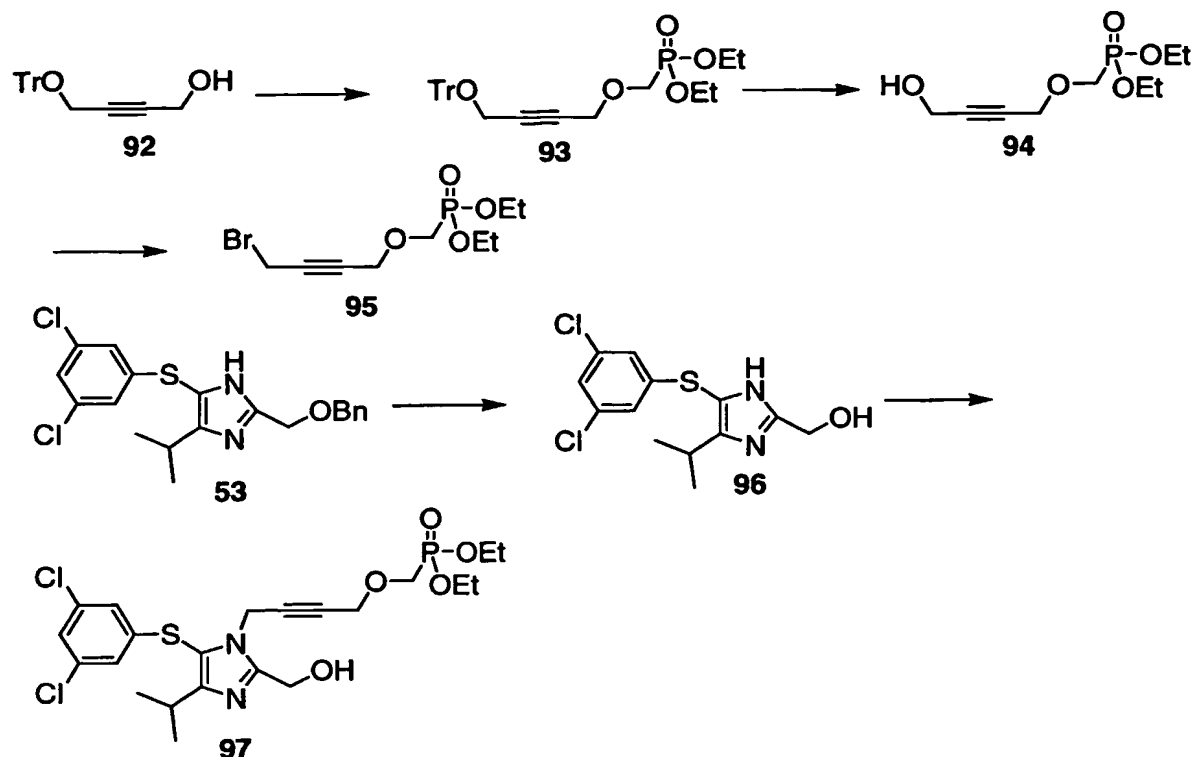
Diethylphosphonate **93**: A solution of alcohol **92** (200 mg, 0.609 mmol) in THF (5 mL) was treated with 60% NaH in mineral oil (37 mg, 0.914 mmol) at 0°C. After the reaction mixture was stirred for 5 min at 0°C, trifluoro-methanesulfonic acid diethoxy-

5   phosphorylmethyl ester (219 mg, 0.731 mmol) was added in THF (3 mL). After the reaction mixture was stirred for an additional 30 min, the mixture was quenched with sat. NH₄Cl and extracted with EtOAc. The organic phase was dried over Na₂SO₄, filtered, and evaporated under reduced pressure to give crude diethylphosphonate **93** as a colorless oil.

Alcohol **94**: A solution of diethylphosphonate **93** (291 mg, 0.609 mmol) in CH₂Cl₂ (5

10   mL) was treated with trifluoroacetic acid (0.5 mL). After the reaction mixture was stirred for 30 min at room temperature, the mixture was concentrated under reduced pressure. The crude product was purified on silica gel (eluting 4-5% MeOH/CH₂Cl₂) to give alcohol **94** (135 mg, 94% over 2 steps) as a colorless oil.

Bromide **95**: A solution of alcohol **94** (134 mg, 0.567 mmol) in CH₂Cl₂ (5 mL) was

15   treated with carbon tetrabromide (282 mg, 0.851 mmol) and triphenylphosphine (164 mg, 0.624 mmol). After stirring at room temperature for 1 h, the mixture was partitioned between CH₂Cl₂ and sat. NaHCO₃. The organic phase was dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was purified twice on silica gel (eluting 60-100% EtOAc/hexane, followed by eluting 0-2% MeOH/CH₂Cl₂) to give bromide **95** (80 mg, 47%)

20   as a colorless oil.

Imidazole **96**: A solution of benzyl ether **53** (2.58 g, 6.34 mmol) in EtOH (60 mL) was treated with conc. HCl (60 mL). After the reaction mixture was warmed to 100°C and stirred for 18 h, the mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and sat. NaHCO$_3$. The organic phase was dried over Na$_2$SO$_4$,

5   filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 8-9% MeOH/CH$_2$Cl$_2$) to give imidazole **96** (1.86 g, 93%) as a colorless solid.

Title compound **97**: A solution of imidazole **96** (54 mg, 0.170 mmol) and bromide **95** (56 mg, 0.187 mmol) in THF (3 mL) was treated with powder NaOH (14 mg, 0.340 mmol), lithium

10   iodide (23 mg, 0.170 mmol), and tetrabutylammonium bromide (27 mg, 0.085 mmol) were then added. After stirring at room temperature for 2 h, the mixture was partitioned between EtOAc and sat. NH$_4$Cl. The organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 3-4% MeOH/CH$_2$Cl$_2$) and by preparative thin layer chromatography (eluting 5% MeOH/CH$_2$Cl$_2$) to

15   give alcohol **97** (42 mg, 46%) as a pale yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.13 (bs, 1H), 6.86 (d, 2H), 4.92 (s, 2H), 4.87 (s, 2H), 4.16 (m, 6H), 3.73 (d, 2H), 3.10 (m, 1H), 1.34 (t, 6H), 1.21 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 20.8.

Example 55

97a

20
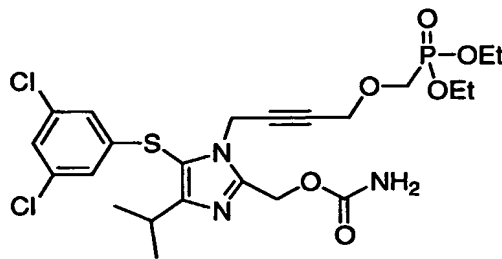
The title compound **97a** was prepared following the sequence of steps described in Example 32 by substituting compound **97a** for compound **68**. Purification of the crude final product on silica gel eluted with 3-4% MeOH/CH$_2$Cl$_2$ provided 13 mg of the title compound.

25   ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.13 (t, 1H), 6.87 (d, 2H), 5.29 (s, 2H), 4.87 (s, 2H), 4.14 (m, 6H), 3.72 (d, 2H), 3.13 (m, 1H), 1.33 (t, 6H), 1.26 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 21.2.

Example 56

101
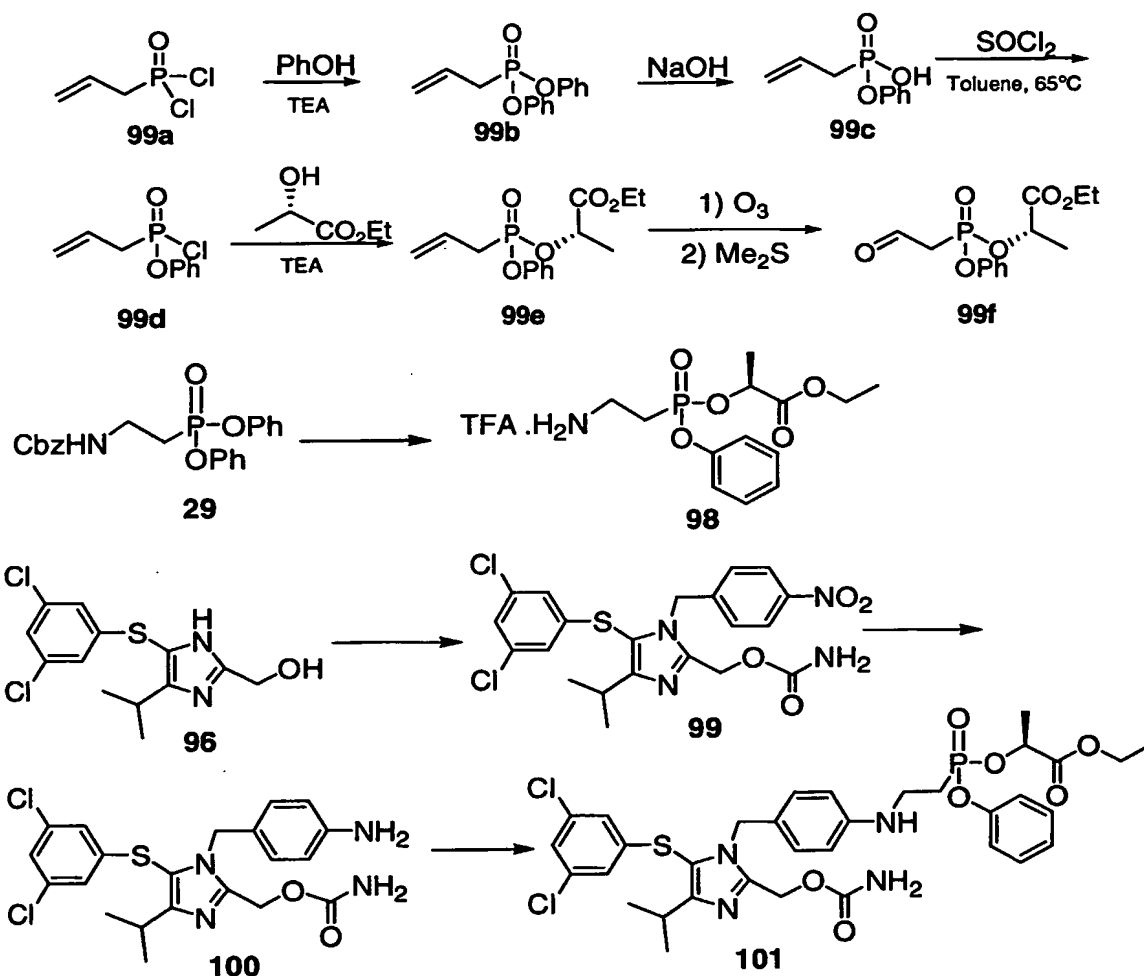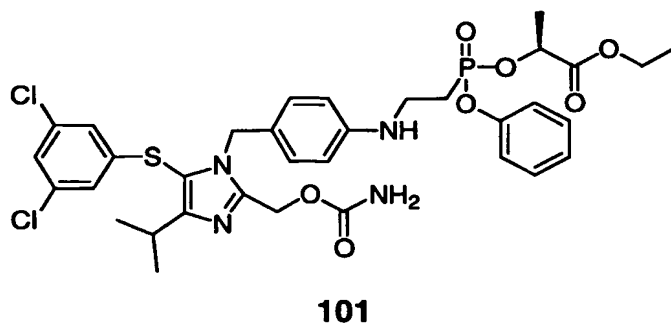
Monophenol Allylphosphonate **99c**: To a solution of allylphosphonic dichloride **99a** (4

g, 25.4 mmol) and phenol (5.2 g, 55.3 mmol) in CH_2Cl_2 (40 mL) at 0°C was added TEA (8.4

mL, 60 mmol). After stirred at room temperature for 1.5 h, the mixture was diluted with

hexane-ethyl acetate and washed with HCl (0.3 N) and water. The organic phase was dried

over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was filtered

through a pad of silica gel (eluted with 2:1 hexane-ethyl acetate) to afford crude product

diphenol allylphosphonate **99b** (7.8 g, containing the excessive phenol) as an oil which was

used directly without any further purification. The crude material was dissolved in CH_3CN (60 mL), and NaOH (4.4N, 15 mL) was added at 0°C. The resulted mixture was stirred at room temperature for 3 h, then neutralized with acetic acid to pH = 8 and concentrated under reduced pressure to remove most of the acetonitrile. The residue was dissolved in water (50 mL) and washed with CH_2Cl_2 (3X25 mL). The aqueous phase was acidified with concentrated HCl at 0°C and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, evaporated and co-evaporated with toluene under reduced pressure to yield desired monophenol allylphosphonate **99c** (4.75 g. 95%) as an oil.

Monolactate Allylphosphonate **99e**: A solution of monophenol allylphosphonate **99c** (4.75 g, 24 mmol) in toluene (30 mL) was treated with $SOCl_2$ (5 mL, 68 mmol) and DMF (0.05 mL). After stirred at 65°C for 4 h, the reaction was completed as shown by ^{31}P NMR. The reaction mixture was evaporated and co-evaporated with toluene under reduced pressure to give mono chloride **99d** (5.5 g) as an oil. A solution of chloride **99d** in CH_2Cl_2 (25 mL) at 0°C was added ethyl (s)-lactate (3.3 mL, 28.8 mmol), followed by TEA. The mixture was stirred at 0°C for 5 min then at room temperature for 1 h, and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2N), the organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford desired monolactate **99e** (5.75 g, 80%) as an oil (2:1 mixture of two isomers).

Aldehyde **99f**: A solution of allylphosphonate **99e** (2.5 g, 8.38 mmol) in CH_2Cl_2 (30 mL) was bubbled with ozone air at −78°C until the solution became blue, then bubbled with nitrogen until the blue color disappeared. Methyl sulfide (3 mL) was added at −78°C. The mixture was warmed up to room temperature, stirred for 16 h and concentrated under reduced pressure to give desired aldehyde **99f** (3.2 g, as a 1:1 mixture of DMSO).

Compound **98** was prepared from compound **29** following the sequence of steps described in Example 22. Compound **99** was prepared from compound **96** following the sequence of steps described in Example 54 and 55, except for substituting 4-nitro benzyl bromide for compound **95**.

Aniline **100**: To a solution of compound **99** (100 mg, 0.202 mmol) in EtOH (2 mL) was added acetic acid (2 mL) and zinc dust (40 mg, 0.606 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was concentrated under reduced pressure. The crude product was purified on silica gel (eluting 5-6% $MeOH/CH_2Cl_2$) to give aniline **100** (43 mg, 41%) as a yellow oil.

Title compound phosphonate **101**: To a solution of aniline **100** (22 mg, 0.042 mmol) and aldehyde **99f** (17 mg, 0.046 mmol) in MeOH (2 mL) was added acetic acid (10 μL, 0.17 mmol) and 4Å molecular sieves (10 mg). After the reaction mixture was stirred for 2 h at room temperature, $NaCNBH_3$ (5 mg, 0.084 mmol) was added. After the reaction mixture was stirred for an additional 4 h at room temperature, the mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and sat. $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluting 5-6% $MeOH/CH_2Cl_2$) to give title compound phosphonate **101** (25 mg, 79%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, 2H), 7.21 (m, 3H), 7.02 (bs, 1H), 6.79 (d, 2H), 6.64 (t, 2H), 6.42 (dd, 2H), 5.21 (s, 2H), 5.10 (s, 2H), 5.02 (m, 1H), 4.75 (bs, 2H), 4.20 (m, 2H), 3.53 (m, 2H), 3.13 (m, 1H), 2.31 (m, 2H), 1.58 (d, 1.5H), 1.38 (d, 1.5H), 1.28 (d, 6H), 1.25 (t, 3H). ^{31}P NMR (300 MHz, $CDCl_3$) δ 28.4, 26.5.

Example 57

105

96

102

103

104

105
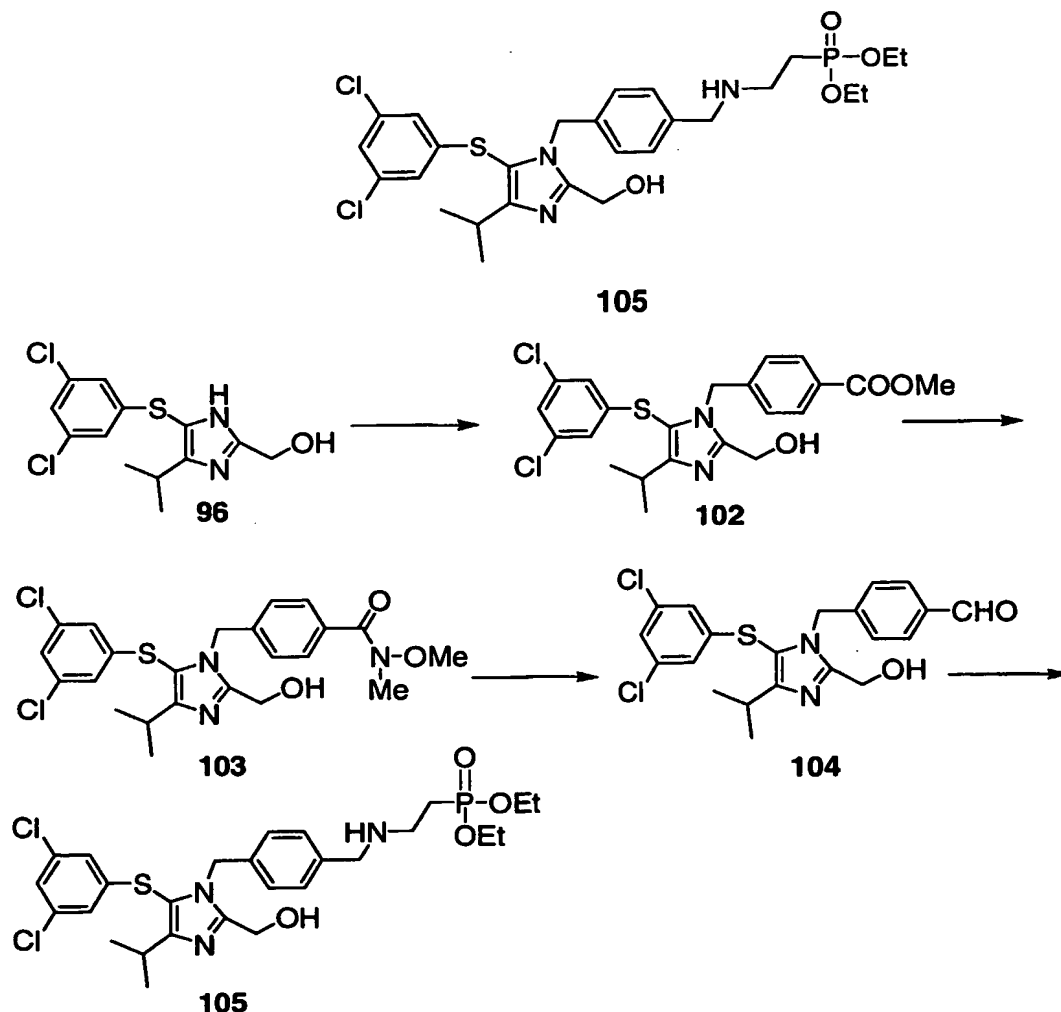
Compound **102** was prepared from compound **96** following the sequence of steps described in Example 54, except for substituting methyl 4-bromomethyl benzoate for compound **95**.

5   Amide **103**: A solution of ester **102** (262 mg, 0.563 mmol) in THF (5 mL) and CH$_3$CN (2 mL) was treated with 1N NaOH (1.13 mL, 1.13 mmol). After the reaction mixture was stirred for 2 h at 60°C, the mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and 1N HCl. The organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was

10   chromatographed on silica gel (eluting 5-10% MeOH/CH$_2$Cl$_2$) to give the carboxylic acid (120 mg, 47%) as a colorless oil. A solution of the above carboxylic acid (120 mg, 0.266 mmol) and N,O-dimethylhydroxylamine (29 mg, 0.293 mmol) in DMF (3 mL) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (61 mg, 0.319 mmol), 1-hydroxybenzotriazole hydrate (43 mg, 0.319 mmol), and triethylamine (55 μL, 0.399 mmol).

15   After the reaction mixture was stirred for 18 h at room temperature, the mixture was partitioned between EtOAc and H$_2$O. The organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 3-4% MeOH/CH$_2$Cl$_2$) to give the amide **103** (107 mg, 81%) as a colorless oil.

Aldehyde **104**: A solution of amide **103** (106 mg, 0.214 mmol) in THF (5 mL) was

20   treated with 1.5M DIBAL-H in toluene (0.43 mL, 0.642 mmol) at 0°C. After the reaction mixture was stirred for 1 h at 0°C, the mixture was quenched with 1M sodium potassium tartrate and stirred for an additional 3 d. The aqueous phase was extracted with EtOAc, and the organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure to give crude aldehyde **104** as a colorless oil.

25   Title compound **105**: To a solution of aldehyde **104** (91 mg, 0.21 mmol) in MeOH (5 mL) was added diethyl(aminoethyl) phosphonate (63 mg, 0.231 mmol), acetic acid (48 μL, 0.231 mmol) and 4Å molecular sieves (10 mg). After the reaction mixture was stirred for 2 h at room temperature, NaCNBH$_3$ (26 mg, 0.42 mmol) was added. After the reaction mixture was stirred for an additional 18 h at room temperature, the mixture was concentrated under

30   reduced pressure. The residue was partitioned between EtOAc and sat. NaHCO$_3$. The organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 5-10% MeOH/CH$_2$Cl$_2$) to give phosphonate **105** (10 mg, 8% over 2 steps) as a colorless oil. ^{1}H NMR (300 MHz, CD$_3$OD) δ

7.15 (d, 2H), 7.10 (t, 1H), 7.06 (d, 2H), 6.65 (t, 2H), 5.34 (s, 2H), 4.73 (s, 2H), 4.09 (m, 4H),

3.68 (s, 2H), 3.12 (m, 1H), 2.83 (m, 2H), 2.04 (m, 2H), 1.30 (t, 6H), 1.24 (d, 6H). ^{31}P NMR

(300 MHz, CD$_3$OD) δ 30.6.

Example 58

106
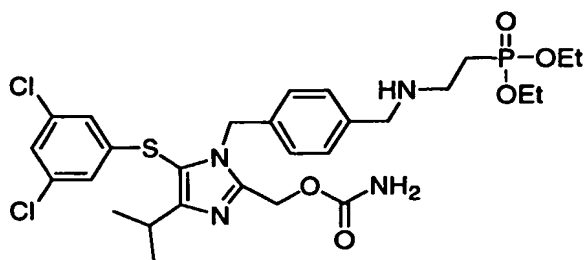
The title compound **106** was prepared following the sequence of steps described in Example 34, except for substituting compound **105** for compound **68**. Purification of the crude final product on preparative thin layer chromatography eluted with 7% MeOH/CH$_2$Cl$_2$ provided 6 mg of the title compound. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.15 (d, 2H), 7.02 (bs, 1H), 6.88 (d, 2H), 6.67 (t, 2H), 5.21 (s, 2H), 5.17 (s, 2H), 4.76 (bs, 2H), 4.08 (m, 4H), 3.70 (s, 2H), 3.15 (m, 1H), 2.86 (m, 2H), 1.97 (m, 2H), 1.31 (t, 6H), 1.29 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 30.6.

Example 59

108

104

107
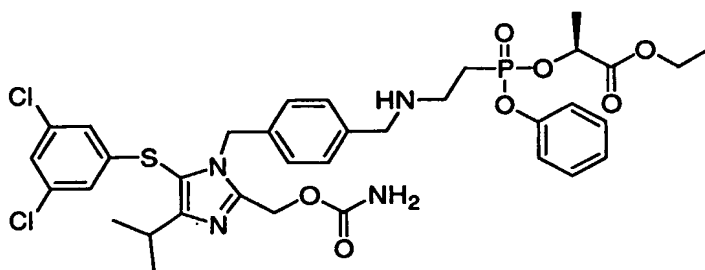
108
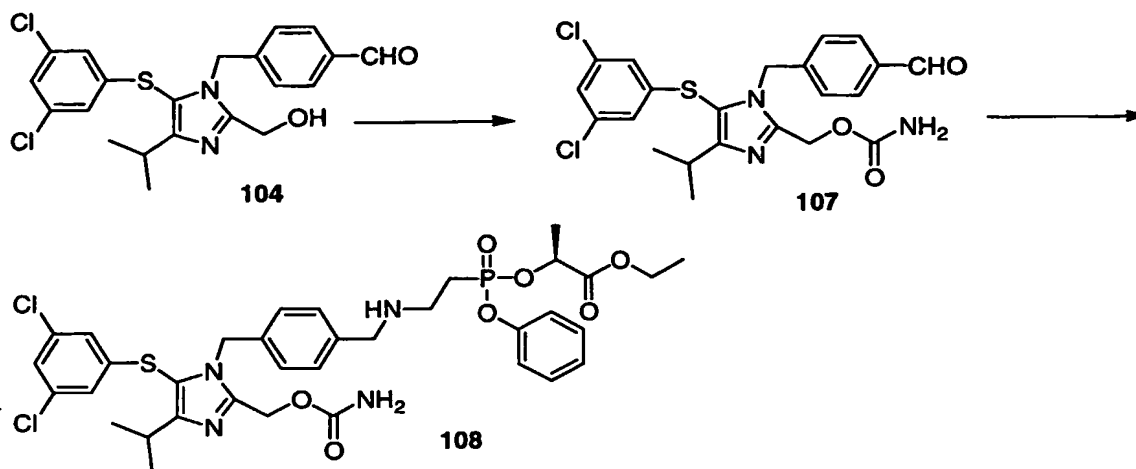
Compound **107** was prepared following the sequence of steps described in Example 34, except for substituting compound **104** for compound **68**. The title compound was prepared following the sequence of steps described in Example 58, except for substituting compound **98** for aminoethyl phosphonic acid diethyl ester. Purification of the crude final product on preparative thin layer chromatography eluted with 7% MeOH/CH$_2$Cl$_2$ provided 24 mg of the title compound **108**. ^{1}H NMR (300 MHz, CDCl$_3$) (5:1 diastereomeric ratio) δ 7.34 (t, 2H), 7.17 (m, 5H), 7.01 (t, 1H), 6.86 (d, 2H), 6.66 (t, 2H), 5.20 (bs, 4H), 4.96 (m, 1H), 4.63 (bs, 2H), 4.19 (m, 2H), 3.73 (s, 2H), 3.15 (m, 1H), 3.02 (m, 2H), 2.27 (m, 2H), 1.36 (d, 3H), 1.29 (d, 6H) 1.27 (m, 3H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 29.1, 27.4.

Example 60

110

29

109
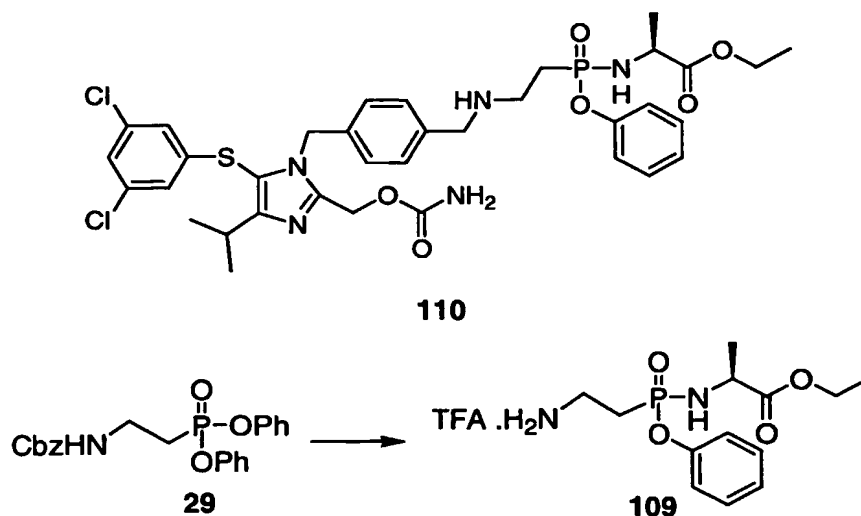
Compound **109** was prepared from compound **29** following the sequence of steps described in Example 22. The title compound was prepared following the sequence of steps described in Example 58, except for substituting compound **109** for aminoethyl phosphonic

acid diethyl ester. Purification of the crude final product on silica gel eluted with 5-6% MeOH/CH$_2$Cl$_2$ provided 8 mg of the title compound. ^{1}H NMR (300 MHz, CDCl$_3$) (1.8:1 diastereomeric ratio)δ 7.31 (m, 2H), 7.16 (m, 5H), 7.01 (bs, 1H), 6.88 (d, 2H), 6.66 (bs, 2H), 5.21 (s, 2H), 5.20 (s, 2H), 4.69 (bd, 2H), 4.27 (bt, 1H), 4.12 (m, 3H), 3.75 (m, 2H), 3.16 (m, 1H), 2.99 (m, 2H), 2.11 (m, 2H), 1.30 (d, 6H), 1.22 (m, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 31.3, 30.8.

Example 61

115

111   **112**   **112a**   **112b**

36   **113**

114   **115**
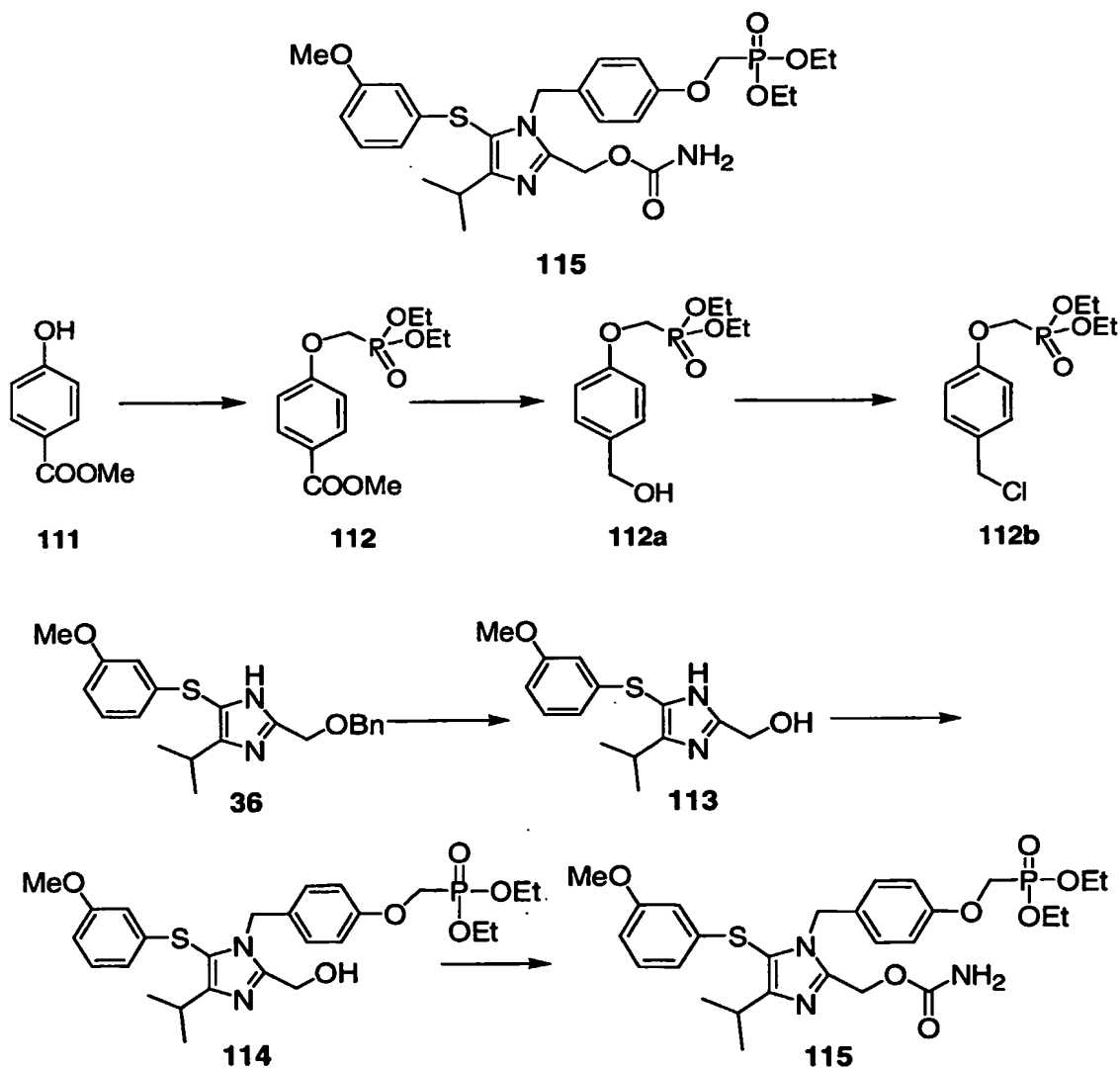
Compound **112**: A solution of methyl 4-hydroxybenzoate **111** (0.977 g, 6.42 mmol) and trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester (2.12 g, 7.06 mmol) in THF (50 mL) was treated with Cs$_2$CO$_3$ (4.18 g, 12.84 mmol). The resulting reaction mixture

was stirred for 1 h at room temperature before it was partitioned between EtOAc and sat. aqueous NH₄Cl and extracted with EtOAc (3x). The organic phase was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure. Purification of the crude product on silica gel (eluted with 60-90% EtOAc/hexane) provided 1.94 g (quantitative) of methyl phosphonobenzoate compound **112** as a clear oil.

Alcohol **112a**: A solution of **112** (1.94 g, 6.42 mmol) in Et₂O (40 mL) was treated with LiBH₄ (0.699 g, 32.1 mmol) and THF (10 mL). After the reaction mixture was stirred for 12 h at room temperature, the mixture was quenched with water and extracted with EtOAc (3x). The organic phase was dried over Na₂SO₄ and evaporated under reduced pressure. The crude product was purified on silica gel (eluted with 2-5% MeOH/CH₂Cl₂) to give 1.48 g (84%) of alcohol compound **112a** as a colorless oil.

Chloride **112b**: A solution of **112a** (315 mg, 1.15 mmol) in MeCN (6 mL) was treated with methanesulfonyl chloride (97.6 µL, 1.26 mmol), TEA (175 µL, 1.26 mmol), LiCl (74.5 mg, 1.72 mmol). After stirring at room temperature for 30 min., the mixture was concentrated under reduced pressure, partitioned between EtOAc and sat. NaHCO₃, and extracted with EtOAc (3x). The organic phase was dried over Na₂SO₄ and evaporated under reduced pressure. Purification of the crude product on silica gel (eluted with 2-4% MeOH/CH₂Cl₂) provided 287 mg (85%) of chloride compound **112b** as a clear pale yellow oil.

Alcohol compound **113**: A solution of benzyl ether **36** (120 mg, 0.326 mmol) in EtOH (2 mL) was treated with conc. HCl (2 mL). After the reaction mixture was refluxed at 100°C for 1 day, the mixture was concentrated under reduced pressure, partitioned between EtOAc and sat. NaHCO₃, and extracted with EtOAc (3x). The organic phase was dried over Na₂SO₄ and evaporated under reduced pressure to provide the crude alcohol compound **113** (90 mg, 99%) as a white solid.

Compound **114**: A solution of alcohol compound **113** (16.8 mg, 0.060 mmol) and chloride compound **112b** (21.1 mg, 0.072 mmol) in THF (1.5 mL) was treated with powder NaOH (3.5 mg, 0.090 mmol), lithium iodide (12.0 mg, 0.090 mmol), and tetrabutylammonium bromide (9.70 mg, 0.030 mmol). After the reaction mixture was stirred at room temperature for 15 h, the mixture was partitioned between EtOAc and sat. NH₄Cl. The organic phase was dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was purified on silica gel (eluted with 3-6% MeOH/CH₂Cl₂) to give compound **114** (19.7 mg, 61%) as a colorless oil.

Title compound **115**: A solution of **114** (19.7 mg, 0.037 mmol) in CH$_2$Cl$_2$ (1 mL) was

treated with trichloroacetyl isocyanate (13.2 μL, 0.111 mmol). After the reaction mixture was

stirred at room temperature for 20 min, 2 mL of CH$_2$Cl$_2$ (saturated with NH$_3$) was added to

the mixture. After stirring at room temperature for 1 h, the mixture was bubbled with N$_2$ for 1

5   h. The mixture was then concentrated under reduced pressure and purified on silica gel

(eluted with 4-6% MeOH/CH$_2$Cl$_2$) to give the titled compound **115** (18.5 mg, 87%) as a clear

oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.09 (t, 1H), 6.90 (d, 2H), 6.78 (d, 2H), 6.63 (dd, 1H),

6.51 (dd, 1H), 6.40 (t, 1H), 5.15 (s, 2H), 5.11 (s, 2H), 4.70 (b, 2H), 4.21 (m, 6H), 3.70 (s,

3H), 3.22 (m, 1H), 1.36 (t, 6H), 1.29 (d, 6H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 19.2.

10

Example 62

118

15
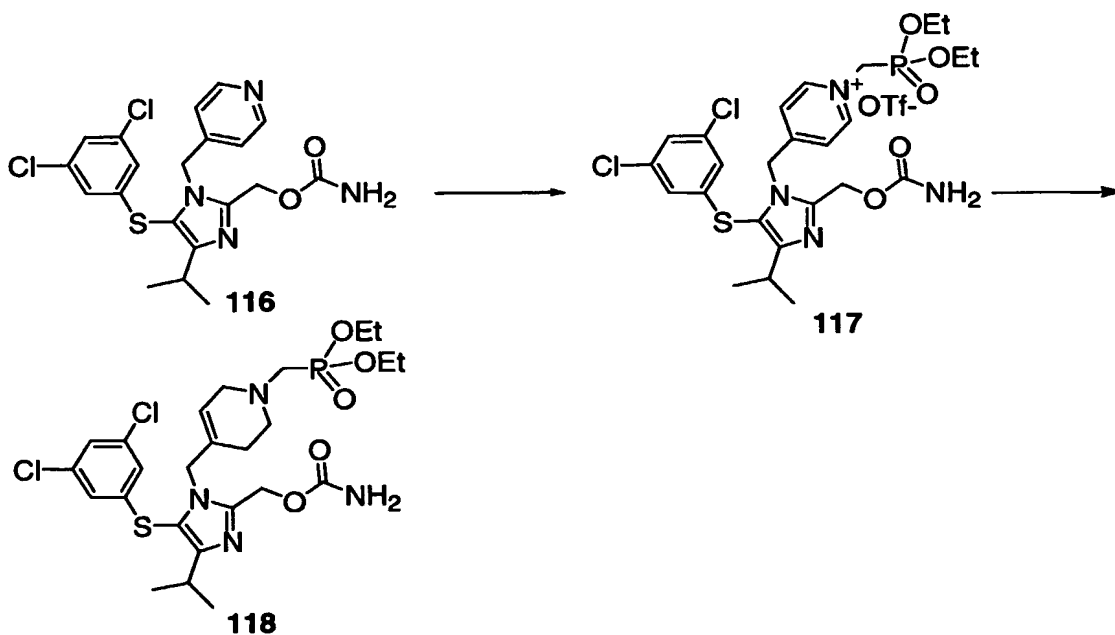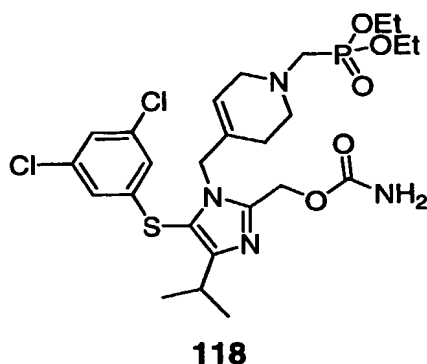
A suspension of compound **116** (15mg, 0.03mmol) in acetone d-6 was treated with trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester (12mg, 0.04 mmol). The solution was stirred overnight at ambient temperature. Concentration afforded compound **117**. Compound **117** (22mg, 0.03mmol) was suspended in EtOH (2mL) and an excess of

5   sodium borohydride(15mg, 0.39mmol) was added. The solution was stirred at room temperature. After 30 minutes, sodium borohydride (15mg, 0.39mmol) was added again. Acetic acid (1ml) in EtOH was added 2 hours later followed by the addition of sodium borohydride (15mg, 0.39mmol). After 30 minutes, the solution was concentrated. The residue was dissolved in saturated aqueous $NaHCO_3$ and extracted with EtOAc (x3). The

10 organic layers were washed with brine and dried over $MgSO_4$. The solution was filtered, concentrated and purified using a TLC plate (5% CH_3OH/CH_2Cl_2) to give 14 mg (80%) of the desired product. ^1H NMR ($CDCl_3$, 500mHz): 7.13 (s, 1H), 6.83 (s, 2H), 5.16 (s, 2H), 5.01 (s, 1H), 4.51 (s, 2H), 4.14 (m, 4H), 3.15 (m, 1H), 3.00 (s, 2H), 2.80 (d, 2H), 2.68 (t, 2H), 1.97 (s, 2H), 1.33 (t, 6H), 1.29 (d, 6H).

15
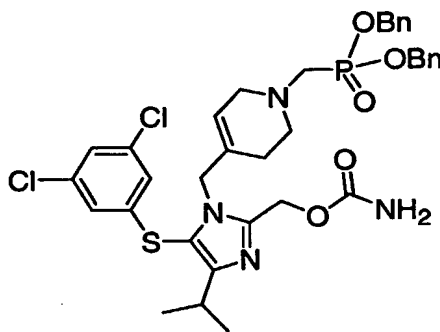
Example 63

119

Title compound **119** was prepared following the sequence of steps described in

20 Example 62 by substituting trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester for trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester. Purification of the crude final product on silica gel eluted with (2.5% - 5% CH_3OH/CH_2Cl_2) provided 71 mg (65%) of the title compound. ^1H NMR ($CDCl_3$, 500 MHz): 7.35 (s, 10H), 7.11 (s,1H) 6.82 (s, 2H), 5.16 (s, 2H), 5.04 (d, 4H), 4.99 (s, 1H), 4.49 (s, 2H), 3.15 (m, 1H), 2.96 (s, 2H), 2.81

25 (d, 2H), 2.63 (t, 2H), 1.91 (s, 2H), 1.29ppm(d, 6H).

Example 64

120
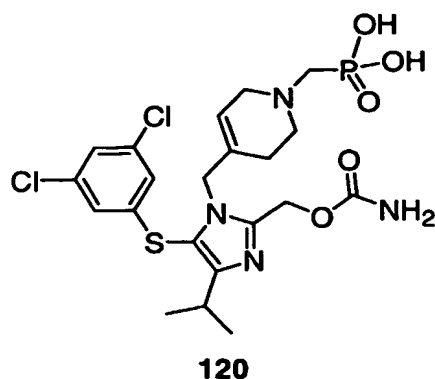
Compound **119** was stirred in 4M HCl/dioxane overnight at ambient temperature. The mixture was concentrated and purified using HPLC (20% CH_3CN/H_2O) to provide 20 mg of

5   the title compound **120**. ^1H NMR (CD_3OD_3, 500 MHz) 7.33 (s,1H) 7.00 (s, 2H), 5.22 (s, 2H), 5.12 (s, 1H), 4.79 (s, 2H), 3.80 (s, 2H), 3.49 (s, 2H), 3.23 (m, 2H), 3.21 (m, 1H), 2.40 (s, 2H), 1.28 (d, 6H).

Example 65

121

10
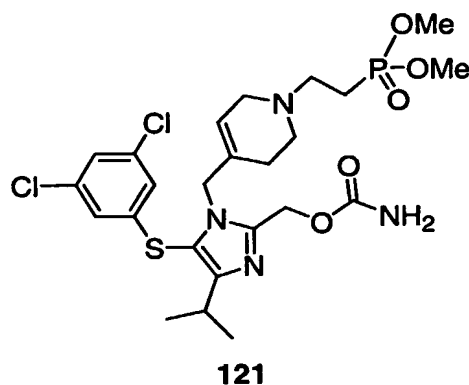
Compound 121 was prepared following the sequence of steps described in Example 62 by substituting trifluoro-methanesulfonic acid dimethoxy-phosphorylethyl ester for trifluoro-methanesulfonic acid diethoxy-phosphorylmethyl ester. Purification of the crude final product

15   on TLC plate eluted with (5% CH_3OH/CH_2Cl_2) provided 11 mg (65%) of the title compound. ^1H NMR ($CDCl_3$, 500 MHz): 7.34 (d, 2H). 7.20 (d, 2H), 7.19 (d,1H) 7.13 (s, 1H), 6.83 (s, 2H), 5.18 (s, 2H), 5.03 (s, 1H), 4.98 (m, 1H), 4.52 (s, 2H), 4.22 (m, 2H), 3.15 (m, 1H), 2.91 (s, 2H), 2.81 (s, 2H), 2.54 (s, 2H), 2.29 (m, 2H), 2.01 (d, 2H), 1.56 (d, 3H), 1.38 (d,3H), 1.28 (q, 3H), 1.28 (d, 6H).

20

Example 66

122
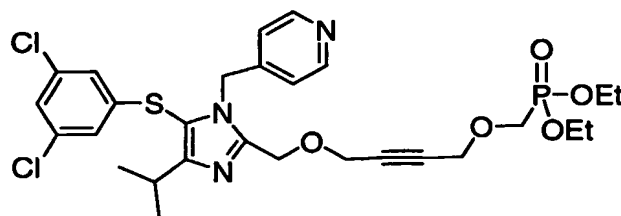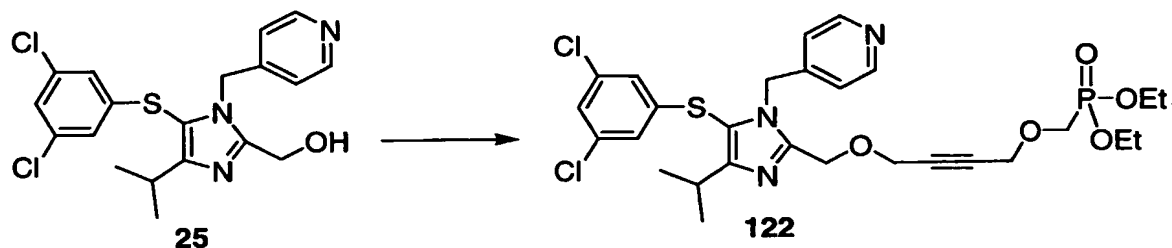
5   **25**   **122**

A solution of **25** (33.2 mg, 0.081 mmol) in DMF (3 mL) under N_2 at 0°C was treated with NaH. After stirring at 0°C for 10 min, **95** (23 mg, 0.077 mmol) was added, and the resulting mixture was slowly raised to room temperature and stirred at room temperature for 8 h. The mixture was then poured into water, and extracted with EtOAc. The combined

10   organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude product was purified on TLC plate (eluted with 3% $MeOH/CH_2Cl_2$) to provide 17.9 mg of the title compound **122**. ^1H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, 2H), 7.04 (t, 1H), 6.88 (d, 2H), 6.67 (d, 2H), 5.24 (s, 2H), 4.67 (s, 2H), 5.02 (m, 1H), 4.27 (bs, 2H), 4.22 (bs, 2H), 4.19 (m, 4H), 3.82 (m, 2H), 3.16 (m, 1H), 1.35 (t, 6H), 1.30 (d, 6H). ^{31}P NMR

15   (300 MHz, $CDCl_3$) δ 20.8.

Example 67: Anti-HIV-1 Cell Culture Assay

        The assay is based on quantification of the HIV-1-associated cytopathic effect by a colorimetric detection of the viability of virus-infected cells in the presence or absence of tested

20   inhibitors. The HIV-1-induced cell death is determined using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) which is converted only by intact cells into a product with specific absorption characteristics as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR (1989) *J Natl Cancer Inst* 81, 577.

Assay protocol for determination of EC50:

1. Maintain MT2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.

2. Infect the cells with the wild-type HIV-1 strain IIIB (Advanced Biotechnologies, Columbia, MD) for 3 hours at 37°C using the virus inoculum corresponding to a multiplicity of infection equal to 0.01.

3. Distribute the infected cells into a 96-well plate (20,000 cells in 100 μL/well) and add various concentrations of the tested inhibitor in triplicate (100 μL/well in culture media). Include untreated infected and untreated mock-infected control cells.

4. Incubate the cells for 5 days at 37°C.

5. Prepare XTT solution (6 ml per assay plate) at a concentration of 2mg/mL in a phosphate-buffered saline pH 7.4. Heat the solution in water-bath for 5 min at 55°C. Add 50 μL of N-methylphenazonium methasulfate (5 μg/mL) per 6 mL of XTT solution.

6. Remove 100 μL media from each well on the assay plate.

7. Add 100 μL of the XTT substrate solution per well and incubate at 37°C for 45 to 60 min in a CO_2 incubator.

8. Add 20 μL of 2% Triton X-100 per well to inactivate the virus.

9. Read the absorbance at 450 nm with subtracting off the background absorbance at 650 nm.

10. Plot the percentage absorbance relative to untreated control and estimate the EC50 value as drug concentration resulting in a 50% protection of the infected cells.

Example 68: Cytotoxicity Cell Culture Assay (Determination of CC50):

   The assay is based on the evaluation of cytotoxic effect of tested compounds using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR (1989) *J Natl Cancer Ins* 81, 577.

Assay protocol for determination of CC50:

1. Maintain MT-2 cells in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics.

2. Distribute the cells into a 96-well plate (20,000 cell in 100 μL media per well) and add various concentrations of the tested compound in triplicate (100 μL/well). Include untreated control.

3. Incubate the cells for 5 days at 37°C.

4. Prepare XTT solution (6 ml per assay plate) in dark at a concentration of 2mg/mL in a phosphate-buffered saline pH 7.4. Heat the solution in a water-bath at 55°C for 5 min. Add 50 µL of N-methylphenazonium methasulfate (5 µg/mL) per 6 mL of XTT solution.

5. Remove 100 µL media from each well on the assay plate and add 100 µL of the XTT substrate solution per well. Incubate at 37°C for 45 to 60 min in a CO_2 incubator.

6. Add 20 µL of 2% Triton X-100 per well to stop the metabolic conversion of XTT.

7. Read the absorbance at 450 nm with subtracting off the background at 650 nm.

8. Plot the percentage absorbance relative to untreated control and estimate the CC50 value as drug concentration resulting in a 50% inhibition of the cell growth. Consider the absorbance being directly proportional to the cell growth.

PETT-like phosphonate NNRTI compounds

The PETT class of compound has demonstrated activity in inhibiting HIV replication. The present invention provides novel analogs of PETT class of compound. Such novel PETT analogs possess all the utilities of PETT and optionally provide cellular accumulation as set forth below.
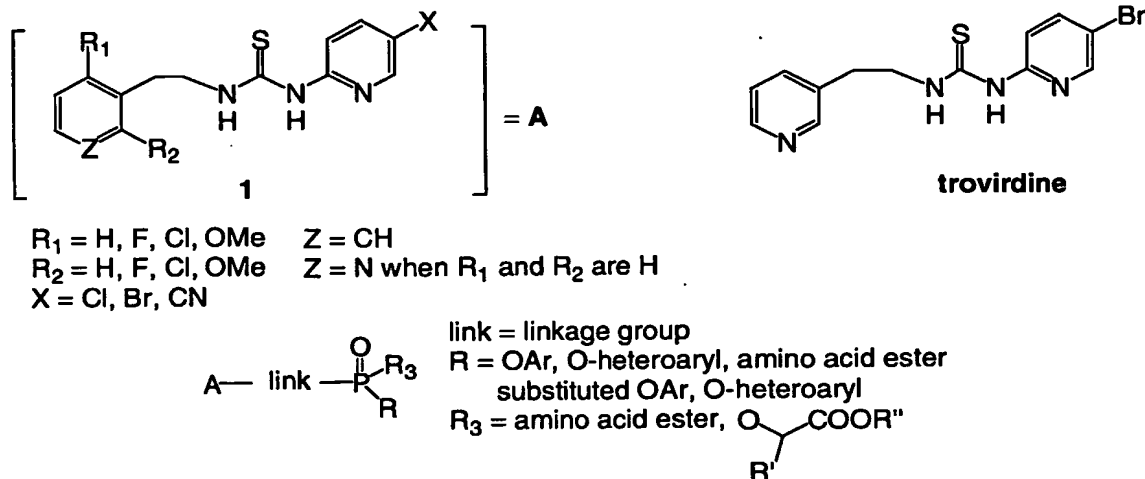
$R_1 = H, F, Cl, OMe$ $Z = CH$
$R_2 = H, F, Cl, OMe$ $Z = N$ when R_1 and R_2 are H
$X = Cl, Br, CN$

link = linkage group
R = OAr, O-heteroaryl, amino acid ester substituted OAr, O-heteroaryl
R_3 = amino acid ester,

The intermediate phosphonate esters required for conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown in Figure 2.
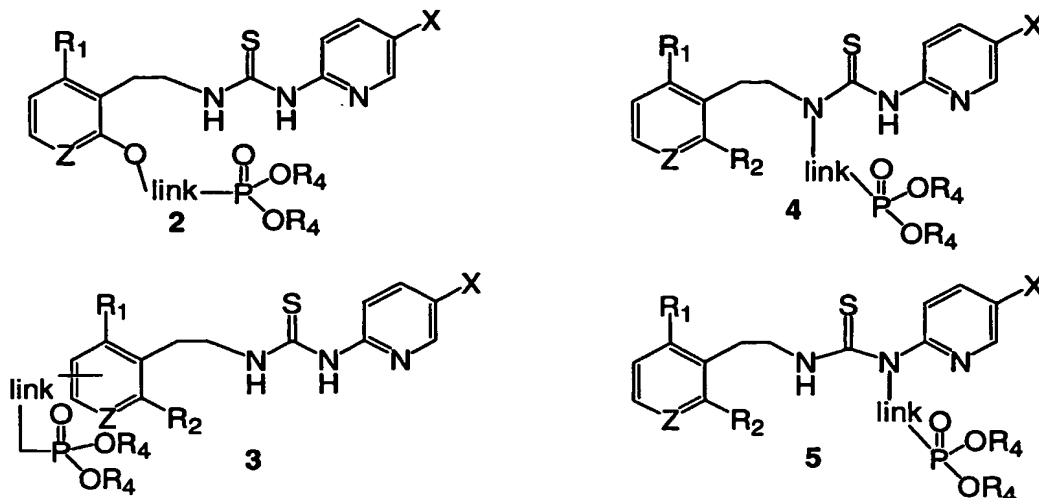
Figure 2

PETT 1 compounds, analogs of trovirdine, are obtained following the procedures described in WO/9303022 and *J. Med. Chem.* **1995**, *38*, 4929-4936 and **1996**, *39*,4261-4274.

5   Preparation of PETT-like phosphonate NNRTI compounds, e.g. phosphonate analog type **2** is outlined in Scheme 1. PETT analog **1a** is obtained following the above mentioned literature procedure. Alkyl group of **1a** is then removed using such as, for example BCl_3 to give phenol **7**, many examples are described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Conversion of **7** to the desired phosphonate analogs is

10   realized by treatment of **7** with the phosphonate reagent **6** under suitable conditions.

For example (Example 1), PETT **1a** is treated with BCl_3 to give phenol **7**. Treatment of **7** with phosphonate **6.1** in the presence of base, for example, Cs_2CO_3, affords the phosphonate **2a.1**. Using the above procedure but employing a different phosphonate reagent **5** in place of **6.1**, corresponding products **2** with different linking groups are obtained.

15   ### Scheme 1
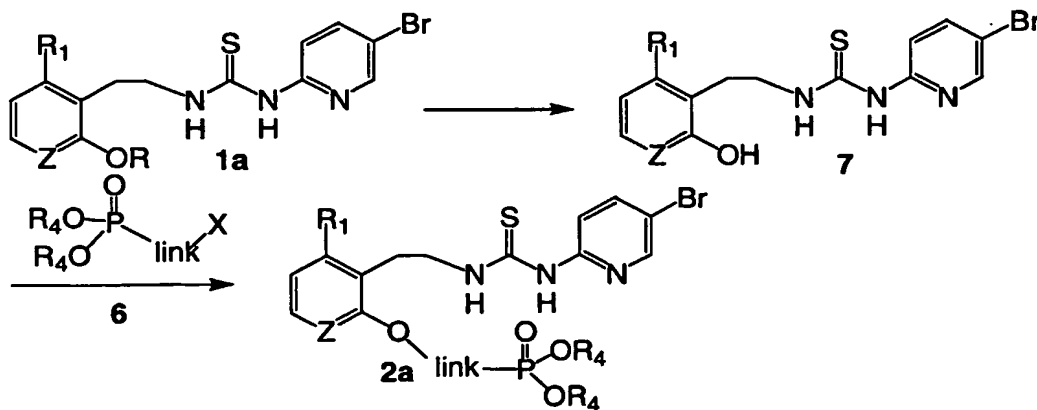
Example 1
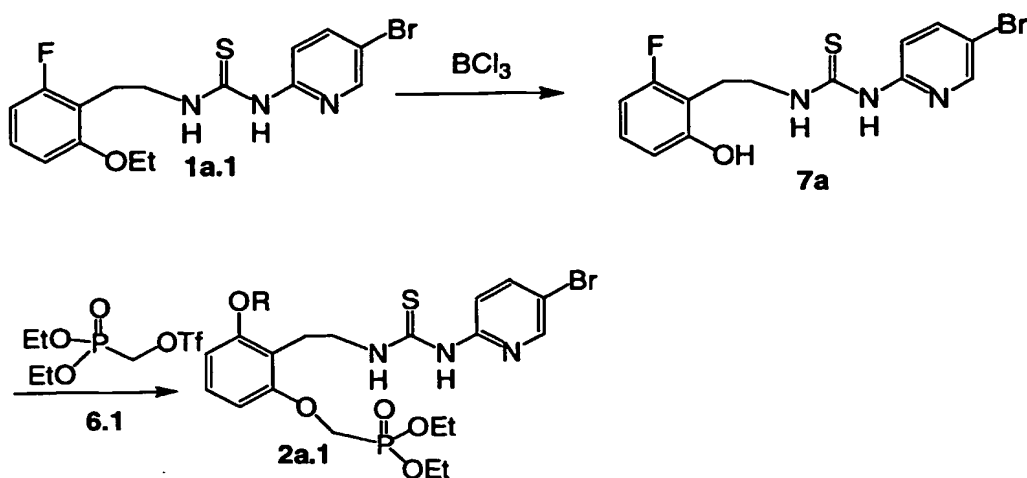
Scheme 2 shows the preparation of phosphonate type 3 in Figure 2. PETT **1b** is

5   obtained as described in WO/9303022 and *J. Med. Chem.* **1995**, *38*, 4929-4936 and **1996**,

39,4261-4274. Alkyl group of **1b** is then removed using such as, for example BCl$_3$ to give

phenol **8**, many examples are described in Greene and Wuts, Protecting Groups in Organic

Synthesis, 3rd Edition, John Wiley and Sons Inc. Conversion of **8** to the desired phosphonate

analogs is realized by treatment of **8** with the phosphonate reagent **6** under suitable conditions.

10   For example (Example 1), PETT **1a** is treated with BCl$_3$ to give phenol **7**. Treatment

of **7** with triflate methyl phosphonic acid diethyl ester **6.1** in the presence of base, for example,

Cs$_2$CO$_3$, affords the phosphonate **2a.1**. Using the above procedure but employing a different

phosphonate reagent **6** in place of **6.1**, corresponding products **3** with different linking groups

are obtained.

15   Scheme 2
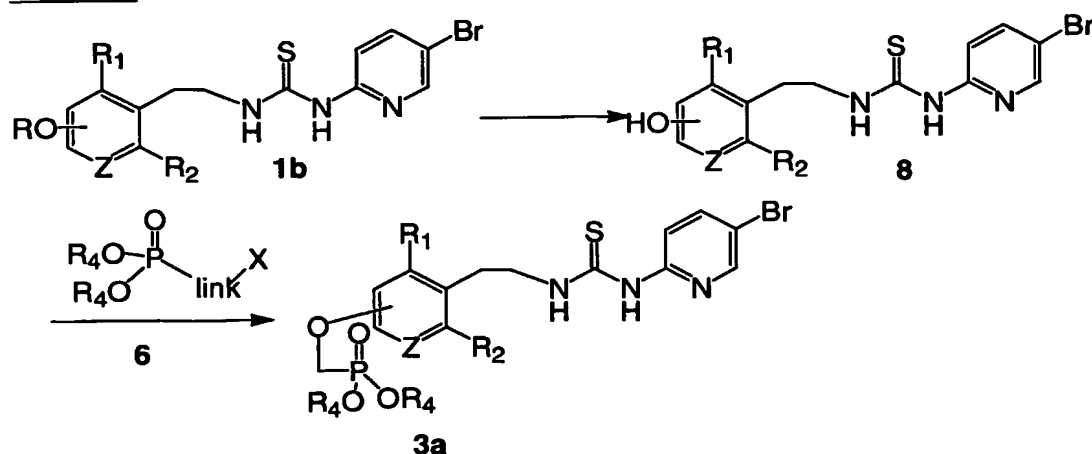
Example 2
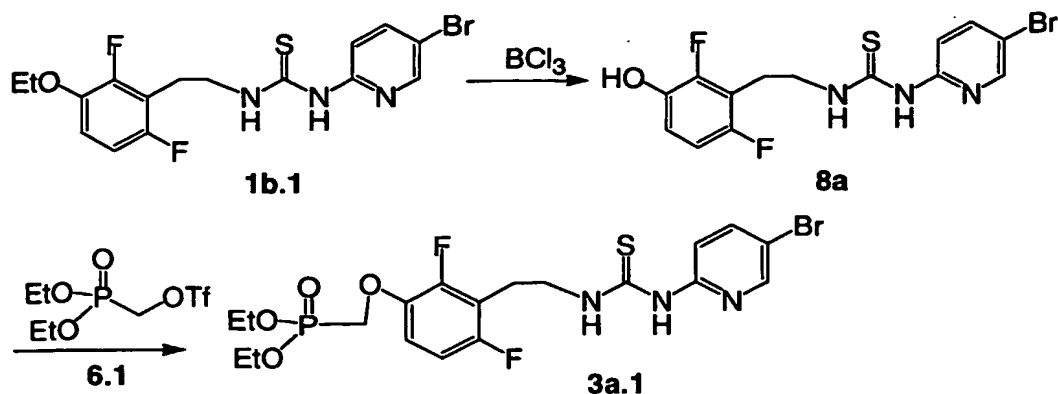
Scheme 3 shows of the preparation of the phosphonate linkage of type **4** and **5** to PETT. PETT **1c** is first treated with a suitable base to remove the thiourea proton, the product is then treated with 1 equivalent of a phosphonate reagent **5** bearing a leaving group such as, for example, bromine, mesyl, tosyl etc to give the alkylated product **4** and **5**. The phosphonates **4** and **5** are separated by chromatography. For example (Example 3), PETT **1**, in DMF, is treated with sodium hydride followed by one equivalent of bromomethyl phosphonic acid dibenzyl ester **6.2** to give phosphonate **4a** and **5a**. Phosphonate product **4a** and **5a** are then separated by chromatography to give pure **4a** and **5a** respectively. Using the above procedure but employing a different phosphonate reagent **5** in place of **6.2**, corresponding products **4** and **5** with different linking groups are obtained.
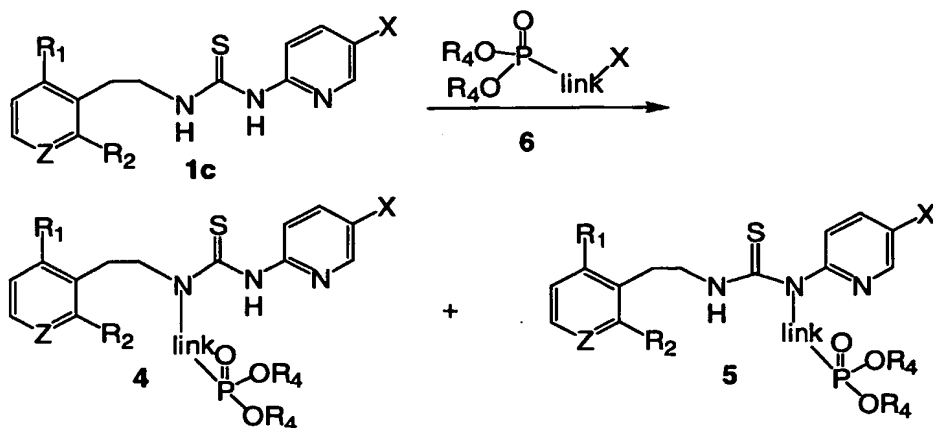
Scheme 3

Example 3

4a   **5a**
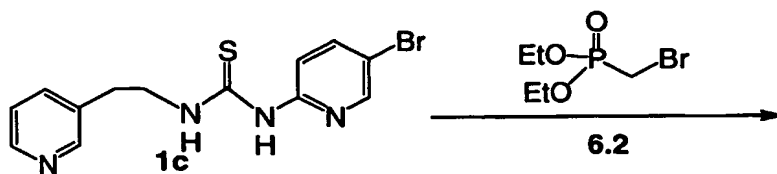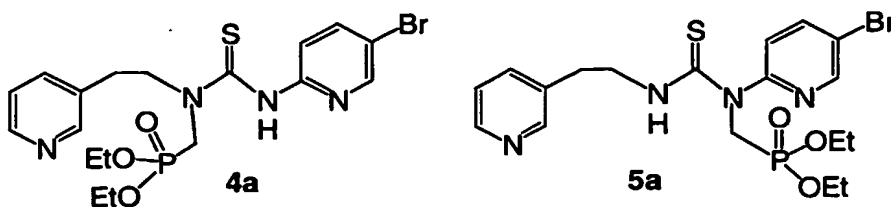
Pyrazole-like phosphonate NNRTI compounds

5   The present invention includes pyrazole-like phosphonate NNRTI compounds and

describes methods for their preparation. Pyrazole-like phosphonate NNRTI compounds are

potential anti-HIV agents.

R_1, R_2, R_3 and R_4, X are defined as
described in Patent WO02/04424.

link = linkage group
R = OAr, O-heteroaryl, amino acid ester
       substituted OAr, O-heteroaryl
R_5 = amino acid ester,

10   Figure 1

         A link group includes a portion of the structure that links two substructures, one of

which is pyrazole class of HIV inhibiting agents having the general formula shown above, the

other is a phosphonate group bearing the appropriate R and R_5 groups. The link has at least

15   one uninterrupted chain of atoms other than hydrogen.

         Pyrazole class of compounds has shown to be inhibitors of HIV RT. The present

invention provides novel analogs of pyrazole class of compound. Such novel pyrazole analogs

possess all the utilities of pyrazoles and optionally provide cellular accumulation as set forth

below.

The intermediate phosphonate esters required for conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown in Figure 2, where R_1, R_2, R_3, R_4 and X are as described in WO02/04424.
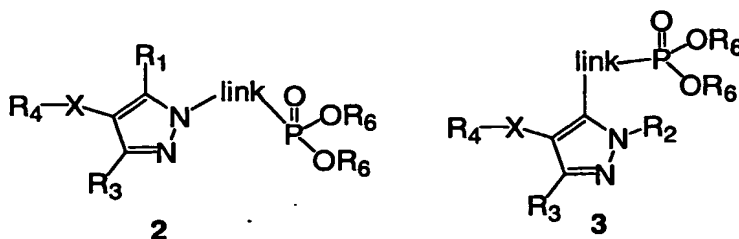
Figure 2

Pyrazole **1** is obtained following the procedures described in WO02/04424. Preparation of phosphonate analog type **2** is outlined in Scheme 1. Pyrazole analog **1a**, which R_2 bears a function group can be used as attaching site for phosphonate prodrug, is obtained as described in the above mentioned literature. Conversion of **1a** to the desired phosphonate analogs is realized by treatment of **2a** with the phosphonate reagent **4** under suitable conditions.

For example (Example 1), treatment of pyrazole **1a.1** with phosphonate **4.1** in the presence of base, for example, Mg(OtBu)$_2$, affords the phosphonate **2a.1**. Using the above procedure but employing a different phosphonate reagent **4** in place of **4.1**, corresponding products **2a** with different linking groups are obtained. Alternatively, activation of the hydroxyl group with bis(4-nitrophenyl) carbonate, following by treatment with amino ethyl phosphonate **4.2** provides phosphonate **2a.2**. Using different phosphonate **4** in place of **4.2** and/or different methods for linking them together affords **2** with different linker.
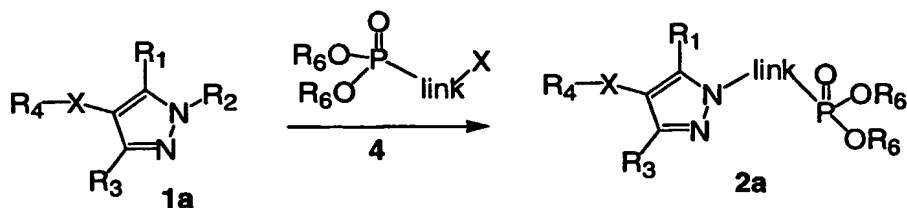
Scheme 1

Example 1
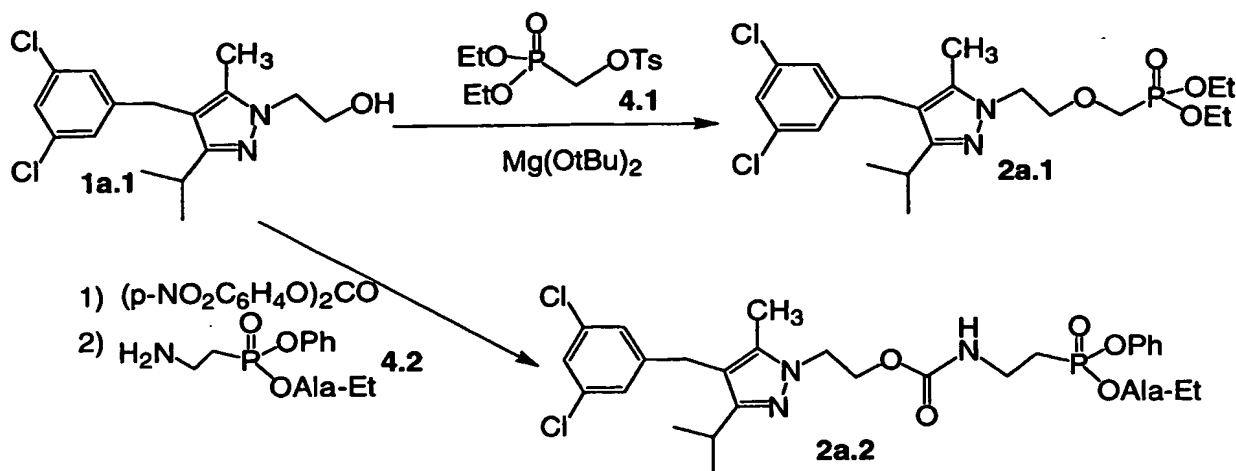
Scheme 2 shows the preparation of phosphonate type 3 conjugate to pyrazole in Figure 2. Pyrazole 1b, bearing a functional group at position R_1 can be used as attaching site for phosphonate prodrug, is obtained as described in WO02/04424. Conversion of 1b to the

5   desired phosphonate 3 analogs is realized by treatment of 1b with the phosphonate reagent 4 under suitable conditions. For example (Example 2), pyrazole 1b reacts with phosphonate 4.3 in the presence of triphenyl phosphine and DEAD in THF, affords the phosphonate 3a.1. Phosphonate 3a.2 is obtained by first reducing the ester to alcohol, and then by treating the resulting alcohol with trichloroacetyl isocyanate, and followed by alumina. Using the above

10   procedure but employing a different phosphonate reagent 4 in place of 4.3, corresponding products 3 with different linking groups are obtained.

<u>Scheme 2</u>
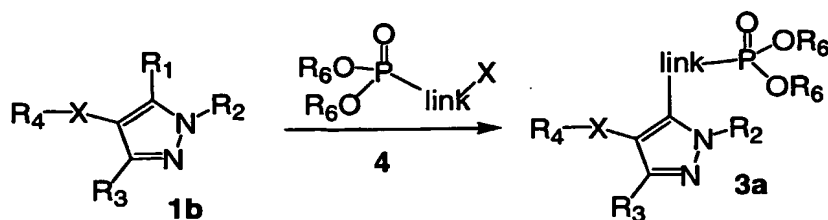
15

<u>Example 2</u>
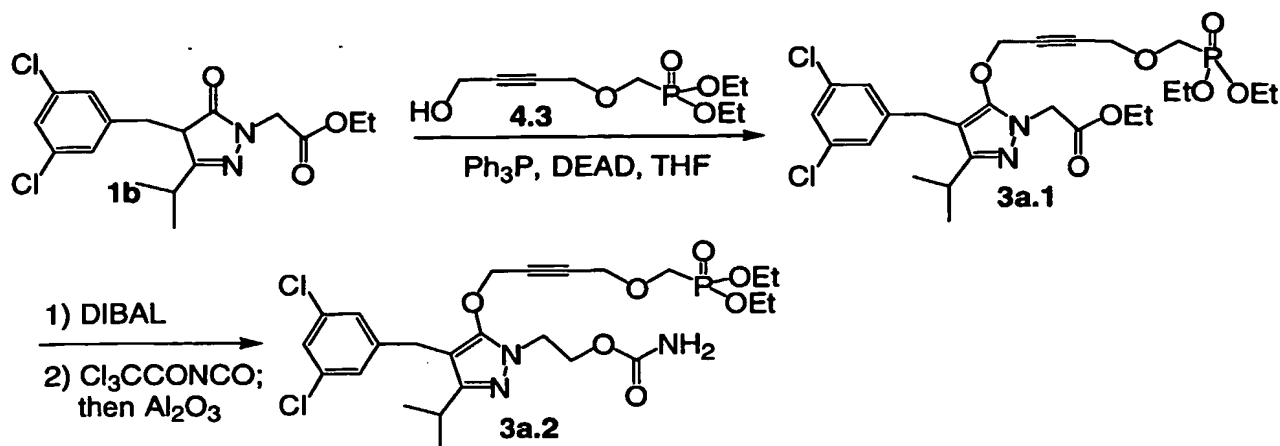
Alternatively, as shown in Example 3, reaction of pyrazolone **1b.1** with a moiety bearing a protected function group which can be used to attach phosphonate, for example

5   benzyl alcohol with a protected hydroxyl or amino group, under Mitsunobu condition affords compound **5**. The protecting group of Z is then removed, and the resulting product is reacted with phosphonate reagent yields phosphonate **3b.1**. Phosphonate **3b.1** is converted to phosphonate **3b.2** following the procedures described Example 2. Reaction of pyrazolone 1b.1with benzyl alcohol **6b** with Ph$_3$P/DEAD produces **5a**. The protecting group MOM- is

10   then removed with TFA to give phenol **5b**. Treatment of phenol with triflate methyl phosphonic acid dibenzyl ester **4a** to give phosphonate **3b.11**, which is also converted to **3b.2** type of compound.

Example 3
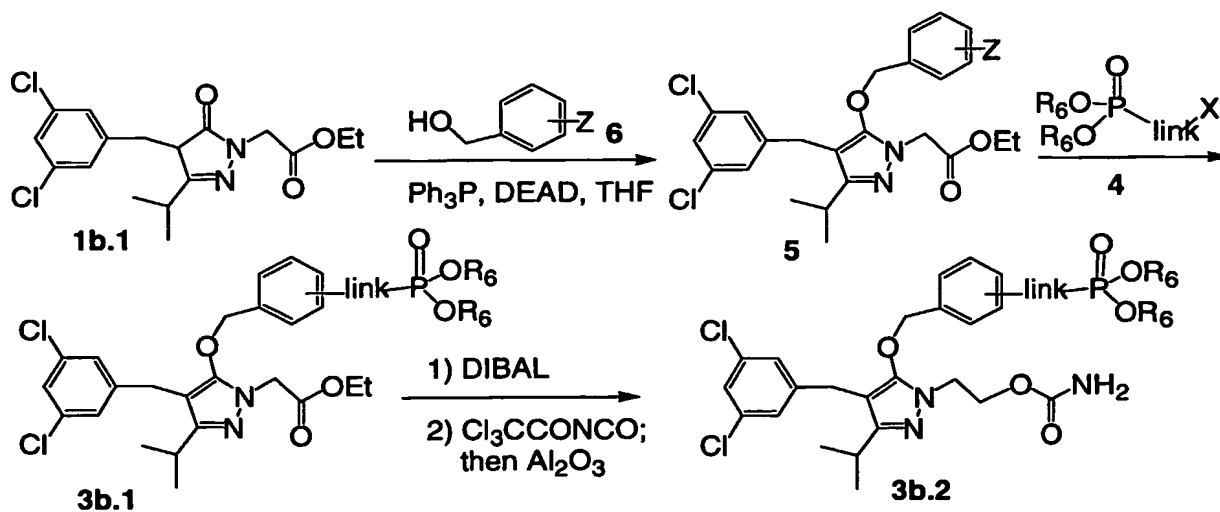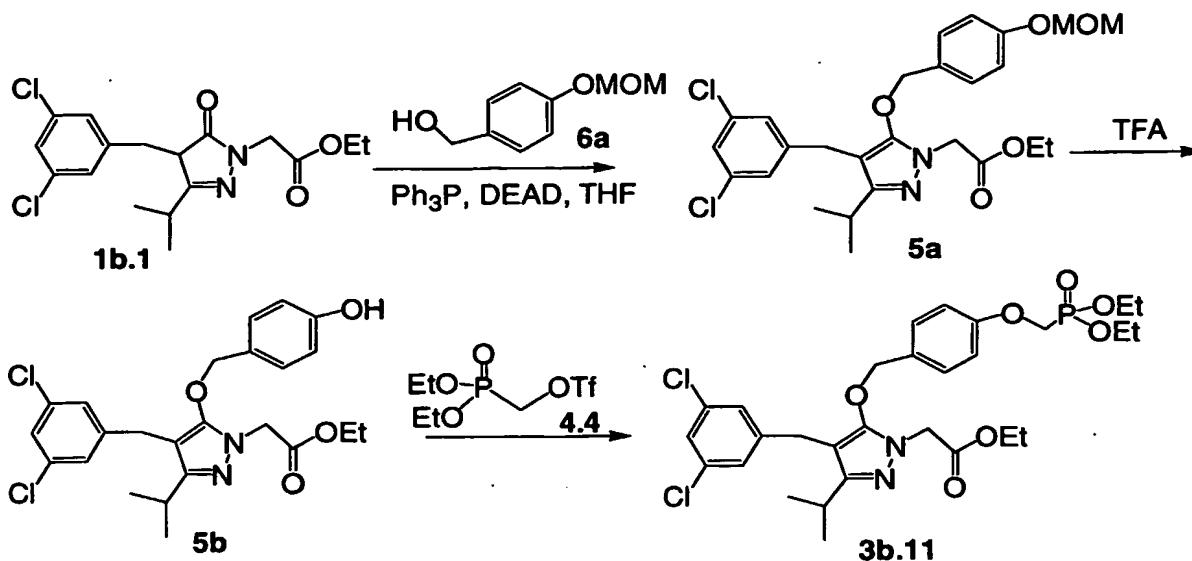
Urea-PETT-like phosphonate NNRTI compounds

The present invention include describes Urea-PETT-like phosphonate NNRTI compounds and methods for their preparation. Urea-PETT-like phosphonate NNRTI compounds are potential anti-HIV agents.
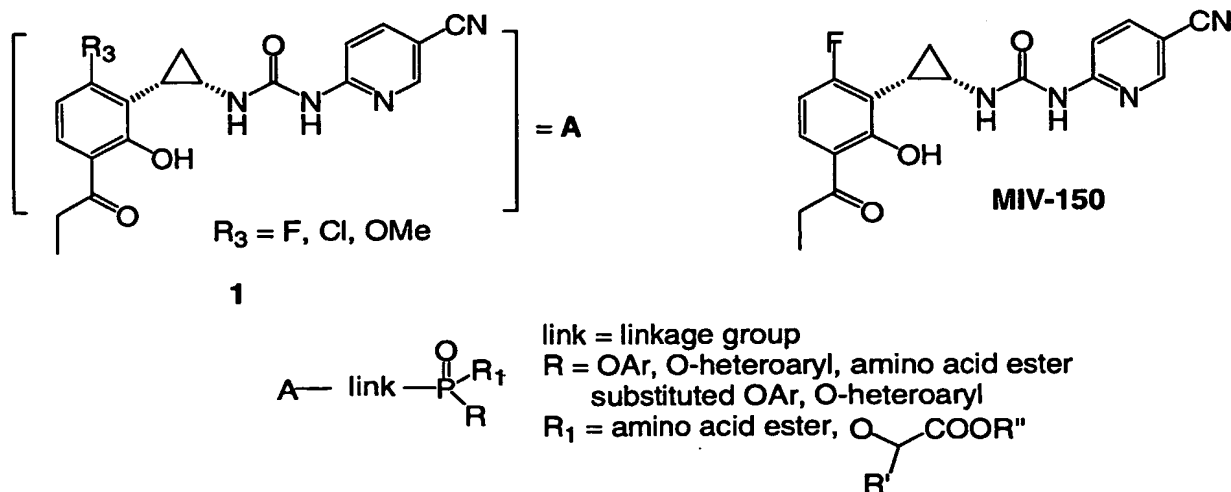
link = linkage group
R = OAr, O-heteroaryl, amino acid ester substituted OAr, O-heteroaryl
R_1 = amino acid ester,

Figure 1

A link group includes a portion of the structure that links two substructures, one of which is urea-PETT class of HIV inhibiting agents having the general formula shown above, the other is a phosphonate group bearing the appropriate R and R1 groups. The link has at least one uninterrupted chain of atoms other than hydrogen.

Urea-PETT class of compound has demonstrated activity in inhibiting HIV replication. The present invention provides novel analogs of urea-PETT class of compound. Such novel

urea-PETT analogs possess all the utilities of urea-PETT and optionally provide cellular accumulation as set forth below.

The intermediate phosphonate esters required for conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown in Figure 2.
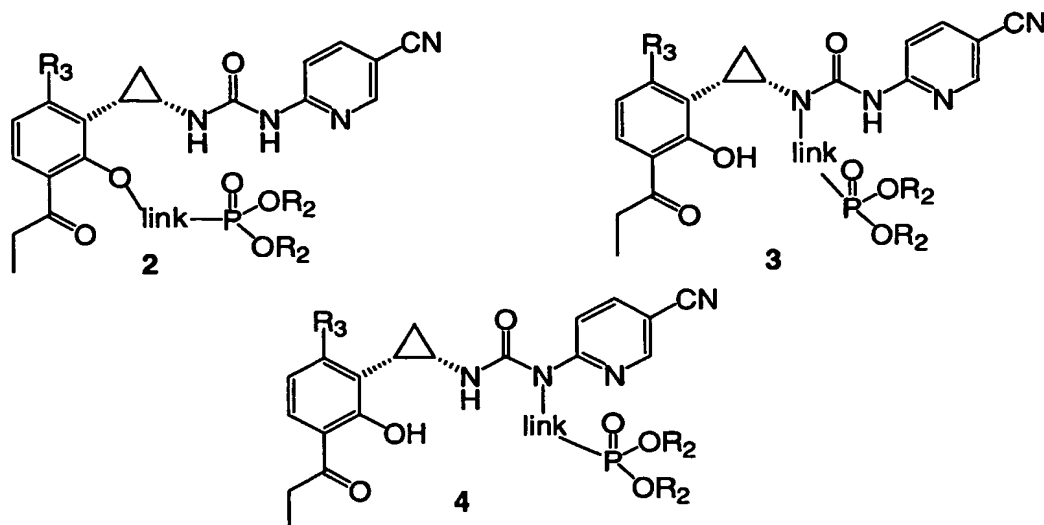
<u>Figure 2</u>

Preparation of phosphonate analog type **2** is outlined in Scheme 1. Urea-PETT **1** is described in US Patent No. 6486183 and *J. Med. Chem.* **1999**, *42*, 4150-4160. Conversion of **1** to the desired phosphonate analogs is realized by treatment of **1** with the phosphonate reagent **5** under suitable conditions. For example (Example 1), urea-PETT **1a** is activated as it *p*-nitro-phenol carbonate by reacting with bis(4-nitrophenyl)carbonate. Reaction of the resulting carbonate with amino ethyl phosphonate **5.1** in the presence of base, for example, Hunig's base, affords the phosphonate **2.1**.

<u>Scheme 1</u>
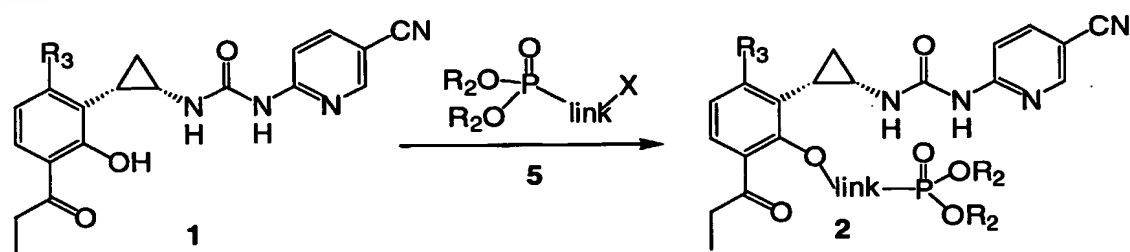
<u>Example 1</u>
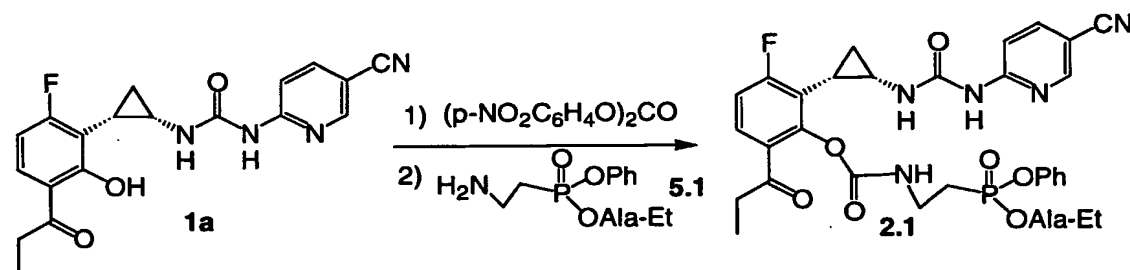
Scheme 2 shows of the preparation of the phosphonate linkage of type **2** and **3** to urea-PETT. The hyroxyl group of urea-PETT **1** is protected with a suitable protecting group, for example, trityl, silyl, benzyl or MOM- etc to give **6** as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. The resulting protected urea-PETT **6** is first treated with a suitable base to remove the urea proton, the product is then treated with 1 equivalent of a phosphonate reagent **5** bearing a leaving group such as, for example, bromine, mesyl, tosyl etc to give the alkylated product **7** and **8**. The phosphonates **7** and **8** are separated by chromatography and independently deprotected using conventional conditions described in Greene and Wuts, Protecting Groups in Organic

Synthesis, 3rd Edition, John Wiley and Sons Inc. p116-121. For example (Example 2), urea-PETT 1 is protected as t-butyl dimethyl silyl ether 6a by reacting with TBSCl and imidazole. Compound 6a, in DMF, is treated with sodium hydride followed by one equivalent of bromomethyl phosphonic acid dibenzyl ester 5.2 to give phosphonate 7a and 8a respectively. phosphonates 7a and 8a are separated by chromatography, and then independently deprotected by treatment with TBAF in an aprotic solvent such as THF or acetonitrile to give 3a and 4a respectively in which the linkage is a methylene group. Using the above procedure but employing a different phosphonate reagent 5 in place of 5.2, corresponding products 3 and 4 with different linking groups are obtained.
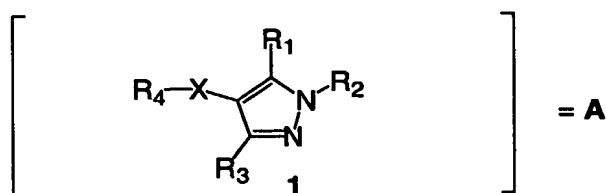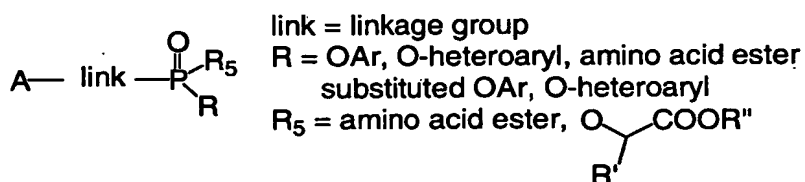
Scheme 2

Example 2

TBSCl

1a → 6a

5.2

7 + 8

TBAF / THF

3a.1 + 4a.1
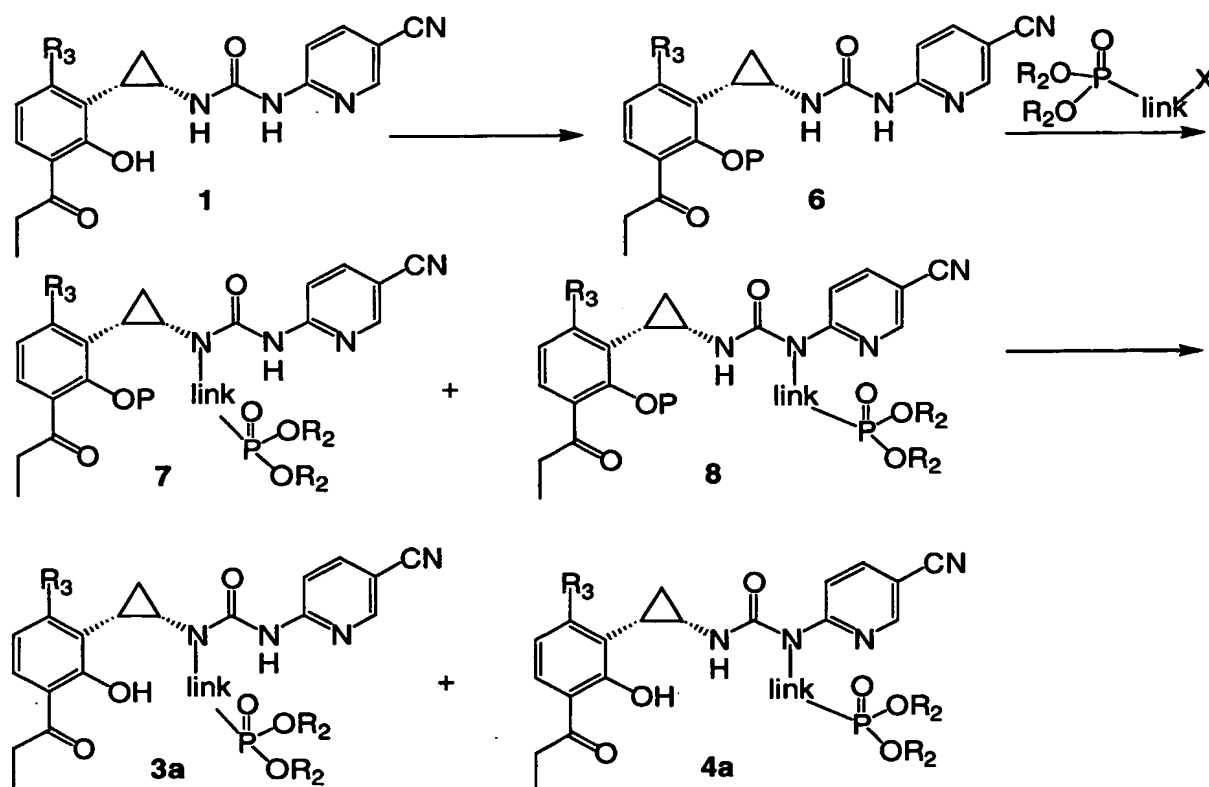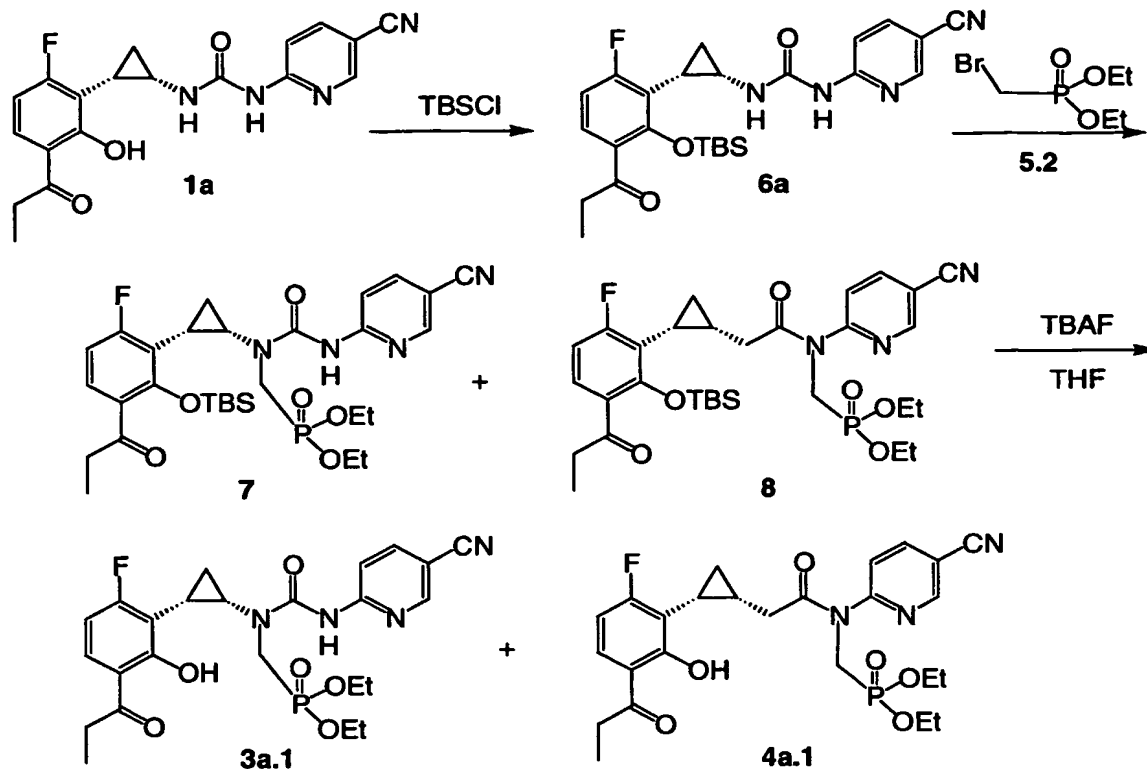
5   Nevaripine-like phosphonate NNRTI compounds

The present invention describes methods for the preparation of phosphonate analogs of nevaripine class of HIV inhibiting agents shown in Figure 1 that are potential anti-HIV agents.

R_2 and R_3 are independently H, C_{1-6} alkyl and C_{1-6} cycloalkyl

= A

A— link—$\overset{O}{\underset{R}{\overset{\|}{P}}}$—$R_1$

link = linkage group
R = OAr, O-heteroaryl, amino acid ester substituted OAr, O-heteroaryl
R1 = amino acid ester, $O\underset{R'}{\diagup}COOR''$

1

Figure 1

A link group includes a portion of the structure that links two substructures, one of which is nevapine class of HIV inhibiting agents having the general formula shown above, the other is a phosphonate group bearing the appropriate R and R1 groups. The link has at least

5   one uninterrupted chain of atoms other than hydrogen. Nevirapine-type compounds are inhibitors of HIV RT, and nevirapine is currently used in clinical for treatment of HIV infection and AIDs. The present invention provides novel analogs of nevirapine class of compound. Such novel nevirapine analogs possess all the utilities of nevirapine and optionally provide cellular accumulation as set forth below.

10   The intermediate phosphonate esters required for conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown in Figure 2.

Figure 2

15
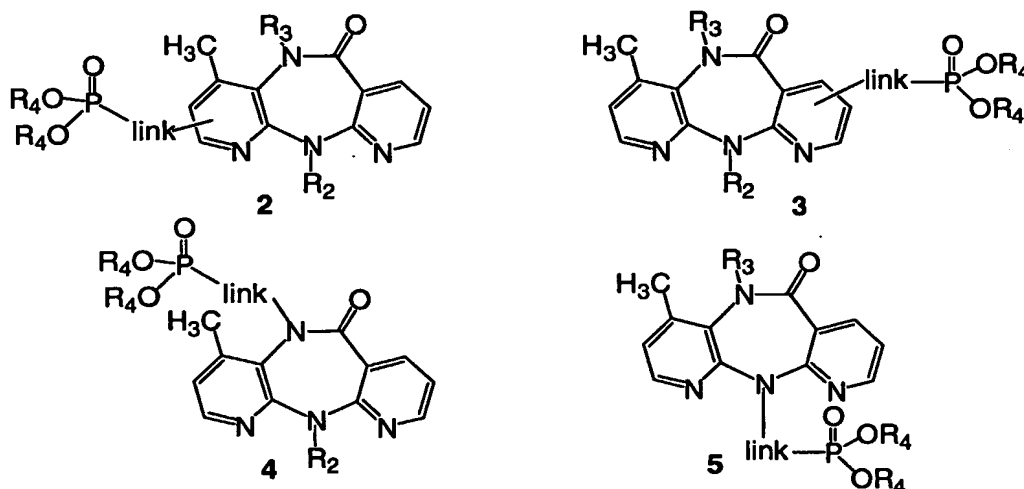
Compound 1 is synthesized as described in US Patent No. 5366972 and *J. Med. Chem.* **1991**, *34*, 2231. Preparation of phosphonate analog 2 is outlined in Scheme 1 and 2. Amide 7 is prepared as described in US Patent No. 5366972 and *J. Med. Chem.* **1998**, *41*, 2960-2971 and 2972-2984. Amide 7 is converted to dipyridodizaepinone 10 following the procedures

20   described in US Patent No. 5366972 and *J. Med. Chem.* **1998**, *41*, 2960-2971 and 2972-2984. Namely, treatment of dipyridine amide 7 with base provides the dipyridodizaepinone 8. Alkylation of the amide N- is achieved with base and alkyls bearing a leaving group, such as, for example, bromide, iodide, mesylate etc. Displacement of chloride with *p*-methoxybenzylamine, followed by removal of the p-methoxybenzyl group affords amine 10.

The amine group serves as the attachment site for introduction of a phosphonate group. Reaction of amine **10** with reagent **6** provides **2** with different linker attached to amine.

Alternatively (Scheme 2), amine **10** is transformed to phenol **11** as described in *J. Med. Chem.* **1998**, *41*, 2972-2984, many examples are also described in R. C. Larock,

5   Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. the hydroxyl group then serves as the linking site for a suitable phosphonate group. Reaction of amine **11** with reagent **6** provides **2** with different linker attached to hydroxyl group. For example (Example 1), amide **7a**, obtained as described in *J. Med. Chem.* **1998**, *41*, 2960-2971 and 2972-2984, is treated with sodium hexamethyldisilazane in pyridine to give diazepinone **9a**. Amine **10a** is

10   synthesized from **9a** by displacement of the chloride with *p*-methoxybenzylamine followed by removal of the protecting group of amine. Diazotization of the amine **10a** and subsequent in situ conversion to hydroxy yields phenol **11a**. Phosphonate with different linker is then able to be attached at the phenol site. For example, the phenol is activated as *p*-nitro-benzyl carbonate, subsequent treatment with amino ethyl phosphonate **6.1** in the presence of Hunig's

15   base affords carbamate **2b.1**.

Scheme 1

20
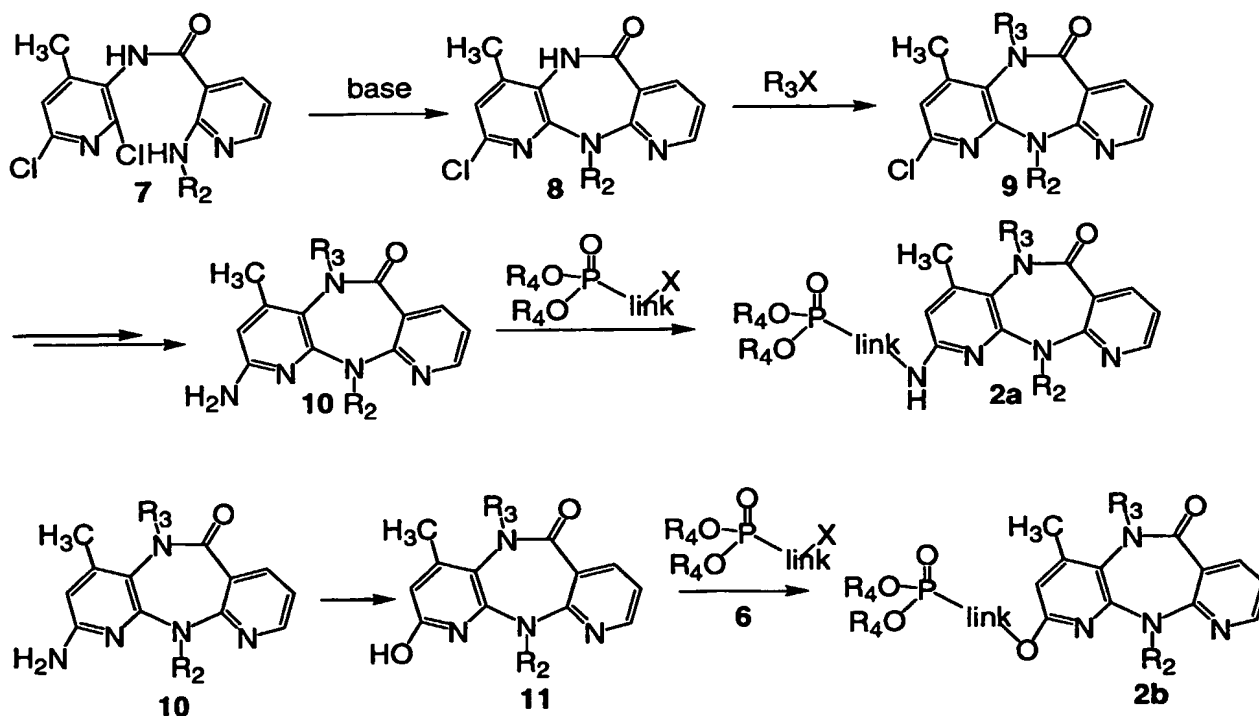
Example 1
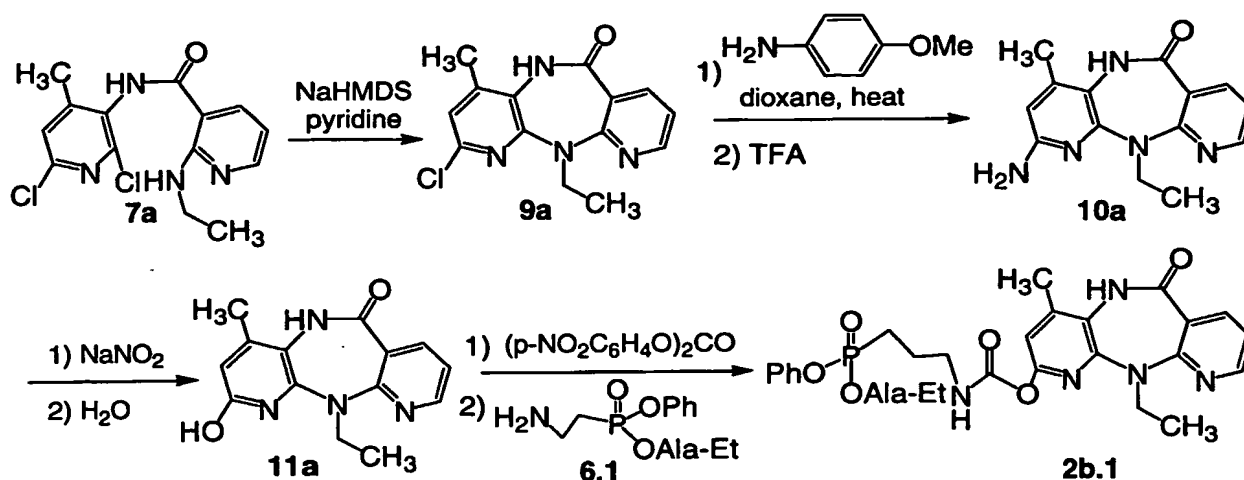
Scheme 2 shows the preparation of phosphonate conjugates compounds type **3** in Figure 2. Diazapinone **13** is obtained from dipyrido amide **7** following the procedure described in *J. Med. Chem.* **1998**, *41*, 2960-2971 and 2972-2984, which is then converted to aldehyde **14** and phenol **14a** following the procedures in the same literature. Aldehyde **14** and phenol **14a** are then converted to **3a** and **3b** respectively by reacting with suitable phosphonate reagents **6**. Amine **14b** is obtained using the method described in *J. Med. Chem.* **1998**, *41*, 2960-2971, which is converted to phosphonate **3c**.

For example (Example 2), amine **14b.1**, obtained by using the procedures described in *J. Med. Chem.* **1998**, *41*, 2960-2971, reacts with phosphonic acid dibenzyl ester **6.2** under reductive amination conditions to give phosphonate **3c.1**.

Scheme 2
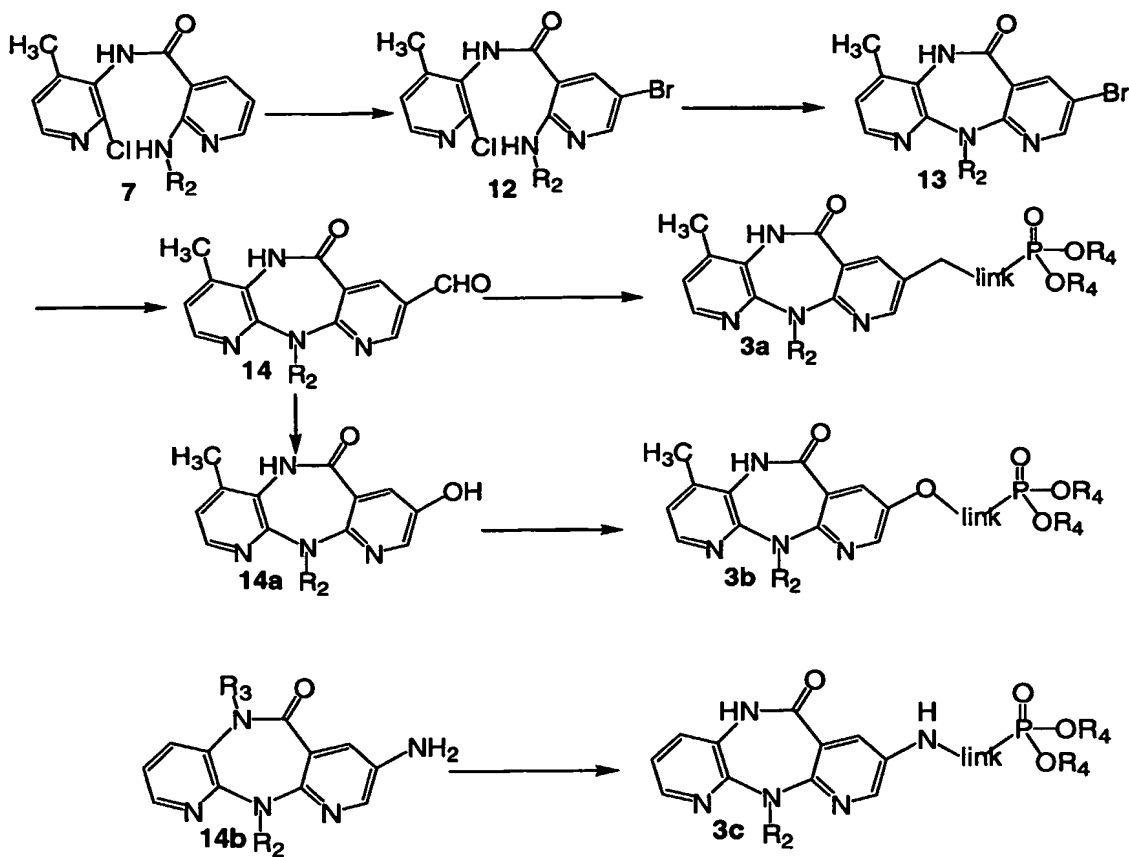
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Example 2
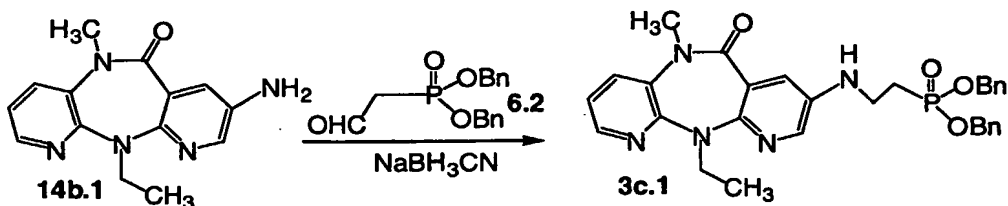
10   Preparation of phosphonate analog type 4 in Figure 2 is shown in Scheme 3.

nevirapine analog 1 is dissolved in suitable solvent such as, for example, DMF or other protic

solvent, and treated with the phosphonate reagent 9, bearing a leaving group, such as, for

example, bromine, mesyl, tosyl, or triflate, in the presence of a suitable organic or inorganic

base, to give phosphonate 4. For example, 1 was dissolved in DMF, is treated with sodium

15   hydride and 1 equivalent of bromomethyl phosphonic acid dibenzyl ester 6.2 to give

phosphonate 4a in which the linkage is a methylene group.

Scheme 3
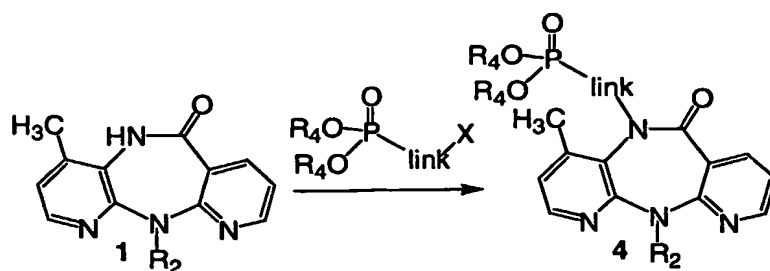
Example 3
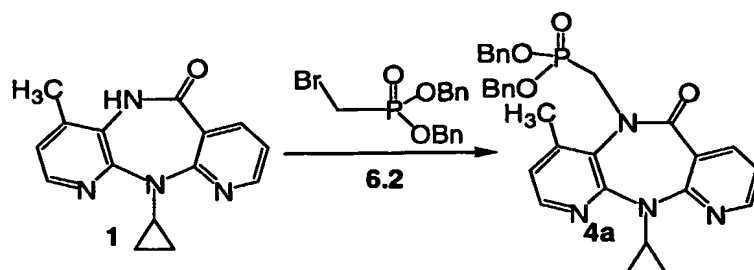
5

Scheme 4 shows the preparation of phosphonate type 5 in Figure 2. Amine 15 is prepared according to the procedures described in US Patent No. 5366972 and *J. Med. Chem.* **1998, 41**, 2960-2971 and 2972-2984. Substituted alkyl amines, which bearing a protected amino or hydroxyl group, or a precursor of amino group, are used in displacement of alkyls

10   described inUS Patent No. 5366972 and *J. Med. Chem.* **1998, 41**, 2960-2971 and 2972-2984, react with the chloropyridine 15 in the presence of base to give amine 16. These alkyl amines include but not limit to examples in Scheme 4. These substituted alkyl amines are obtained from commercial sources by protection of the amino or hydroxyl group with a suitable protecting group, for example trityl, silyl, benzyl etc as described in Greene and Wuts,

15   Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Formation of the diazepinone ring in the presence of a suitable base produces 17. Removal of protecting group or conversion to amine group from a precursor, such as a nitro group, followed by treatment with reagent 6 yield 5a. For example (Example 4), the hydroxyl group of 2-hydroxy ethylamine is protected as its MOM-ether (19). Selective displacement of 2'-chloro

20   substituent of the pyridinecarboxamide ring with substituted ethylamine 19 produce 16a. Formation of the diazepinone ring in the presence of sodium hexamethyldisilazane affords 17a. MOM- is then removed to provide alcohol 18a. The hydroxyl group is then used for attaching the phosphonate group. The alcohol is first converted to carbonate by reacting with bis(4-

nitrobenzyl)carbonate, subsequent treatment of the resulting carbonate with aminoethyl phosphonate **6.2** provides phosphonate **5a.1**.
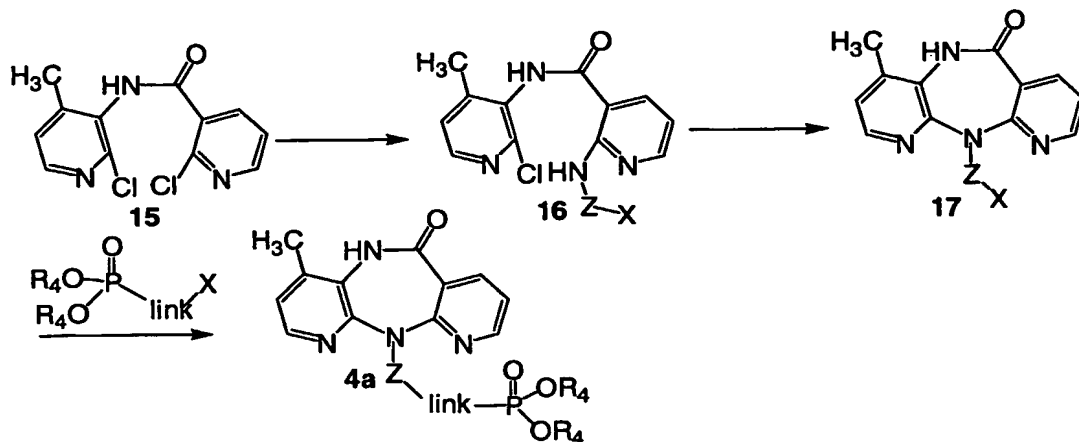
Scheme 5
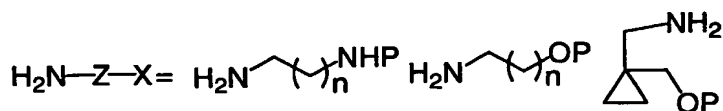
Example 5
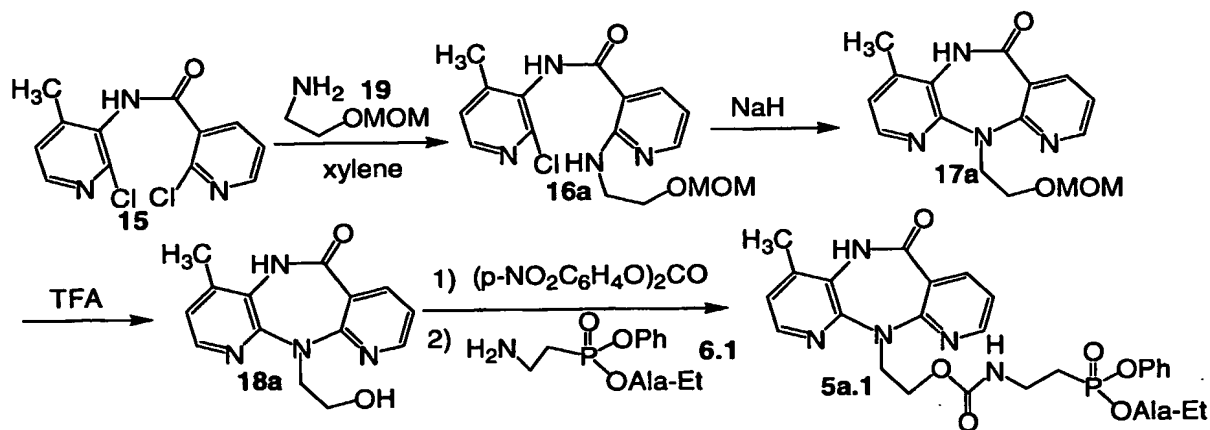
10   Quinazolinone-like phosphonate NNRTI compounds

The present invention describes methods for the preparation of phosphonate analogs of quinazolinones shown in Figure 1 that are potential anti-HIV agents.
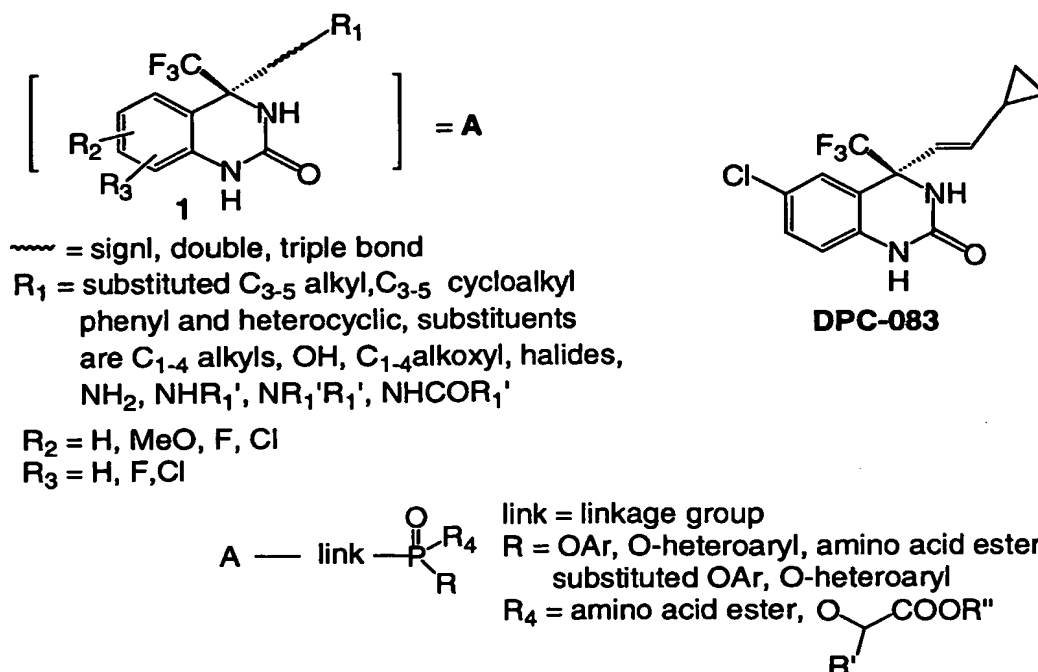
$\sim\sim$ = signl, double, triple bond

R_1 = substituted C_{3-5} alkyl, C_{3-5} cycloalkyl
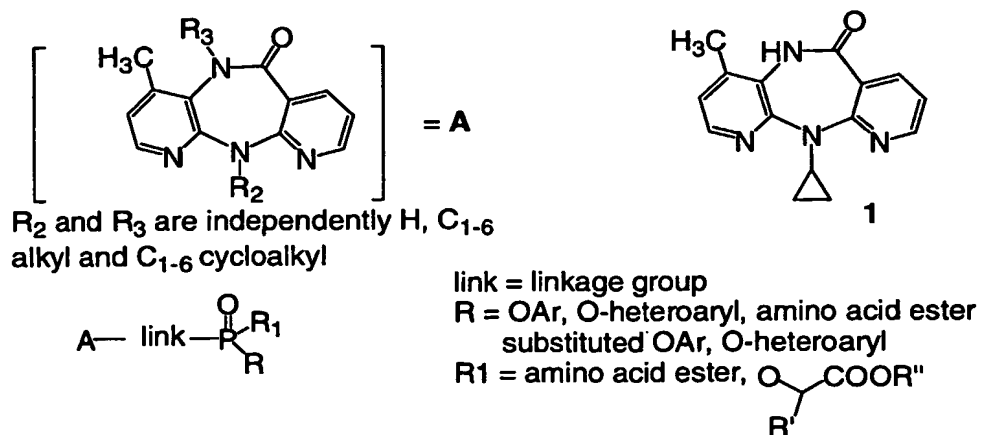phenyl and heterocyclic, substituents
are C_{1-4} alkyls, OH, C_{1-4}alkoxyl, halides,
NH_2, NHR_1', $NR_1'R_1'$, $NHCOR_1'$

R_2 = H, MeO, F, Cl
R_3 = H, F, Cl

DPC-083

A — link — P

link = linkage group
R = OAr, O-heteroaryl, amino acid ester
substituted OAr, O-heteroaryl
R_4 = amino acid ester, O — COOR"

Figure 1

A link group includes a portion of the structure that links two substructures, one of

5   which is quinazolinones having the general formula shown above, the other is a phosphonate

group bearing the appropriate R and R_4 groups. The link has at least one uninterrupted chain

of atoms other than hydrogen.

Quinozolinone class of compound, act as NNRTI, has demonstrated to inhibit HIV

replication. DPC-083, one of representative analogs of this class of compounds, is in clinical

10   phase II studies for treatment of HIV infection and AIDs. The present invention provides

novel analogs of quinozolinone class of compound. Such novel quinozolinone analogs possess

all the utilities of quinozolinone and optionally provide cellular accumulation as set forth

below.

The intermediate phosphonate esters required for conversion into the prodrug

15   phosphonate moieties bearing amino acid, or lactate esters are shown in Figure 2.
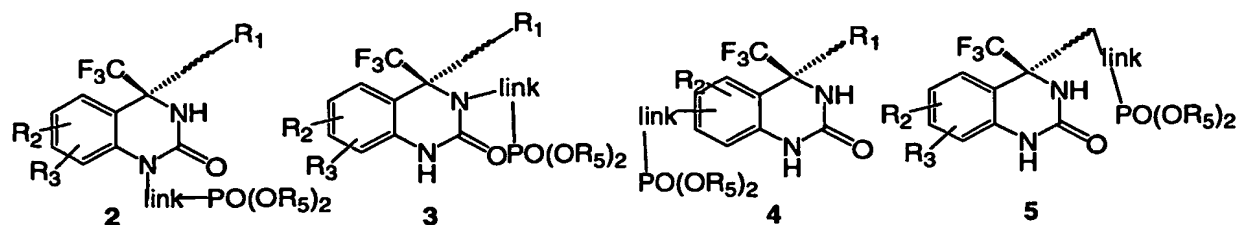
Figure 2

Preparation of phosphonate 2 is outlined in Scheme 1. Quinazolinone 1, synthesized as described in Patent EP0530994, WO93/04047 and US Patent No. 6423718, is dissolved in suitable solvent such as, for example, DMF or other protic solvent is first treated with a

5   suitable base to remove the urea proton, the product is then treated with 1 equivalent of a phosphonate reagent **8** bearing a leaving group such as, for example, bromine, mesyl, tosyl etc to give the alkylated product **2** and **3**. The phosphonates **2** and **3** are separated by chromatography. For example, **1** is dissolved in DMF, is treated with sodium hydride and 1 equivalent of bromomethyl phosphonic acid diethyl ester **8.1** prepared to give quinazolinone

10   phosphonate **2** in which the linkage is a methylene group. Using the above procedure but employing different phosphonate reagents **8** in place of **8.1**, the corresponding products **2** and **3** are obtained bearing different linking group.

Scheme 1

15
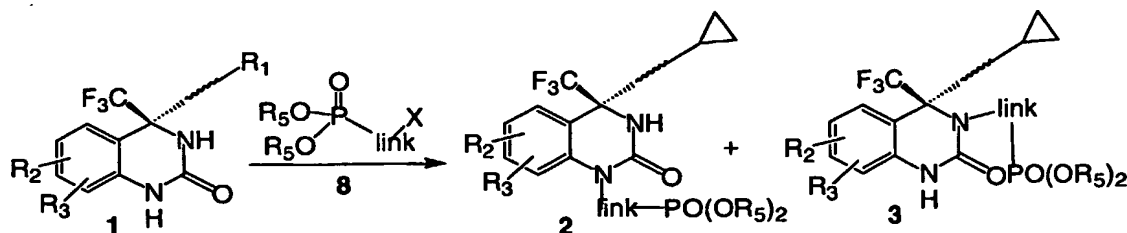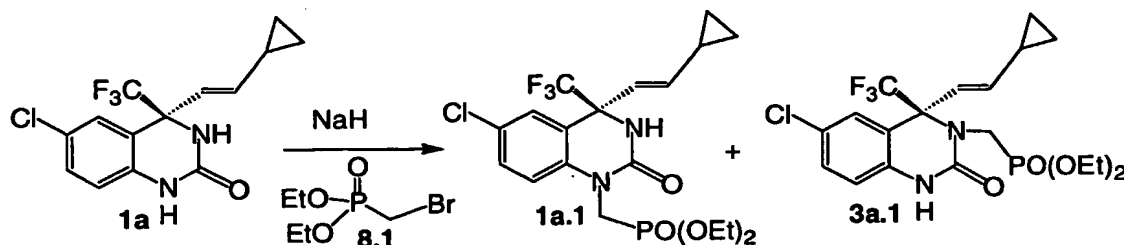
Example 1

20   Scheme 2 shows the preparation of phosphonate analogs type **2** and **3** attached with an alternative way. Quinazolinone **1**, dissolved in a suitable solvent such as, for example, DMF or other protic solvents, is first treated with a suitable base to remove the urea proton, the product is then treated with 1 equivalent of reagent **B**, which bears a leaving group such as, for example, bromine, mesyl, tosyl etc, to give the alkylated product **7a** and **7b**. Compound **B**

25   possesses a protected NH_2 or OH group, or a precursor for them. The alkylated product **7a**

and **7b** are separated by chromatography. Protecting group is then removed, and the resulting alcohol or amine then reacts with reagent **8** to afford **2b** and **3b** respectively.

Alternatively (Scheme 3), alkylation of **1** with bromoacetate provides **9a** and **9b**, which are separated by chromatography. The ester group of **9** is reduced to alcohol to give **10**. The alcohol **11** is also transformed to amine **12** under conventional conditions, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. The hydroxyl group of **10** and amino group of **12** then serve as the attachment site for linking phosphonate to provide **2c**. Similarly, ester **10a** is converted to phosphonate **3c** following the procedures of transformation of **10** to **2c**.
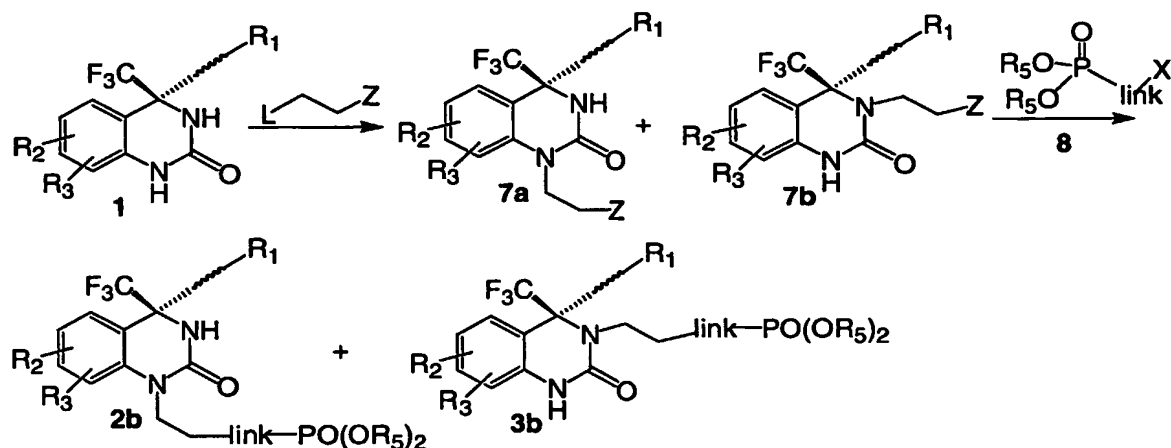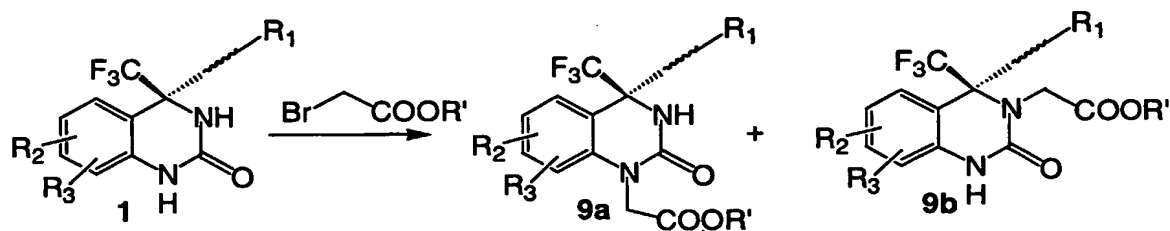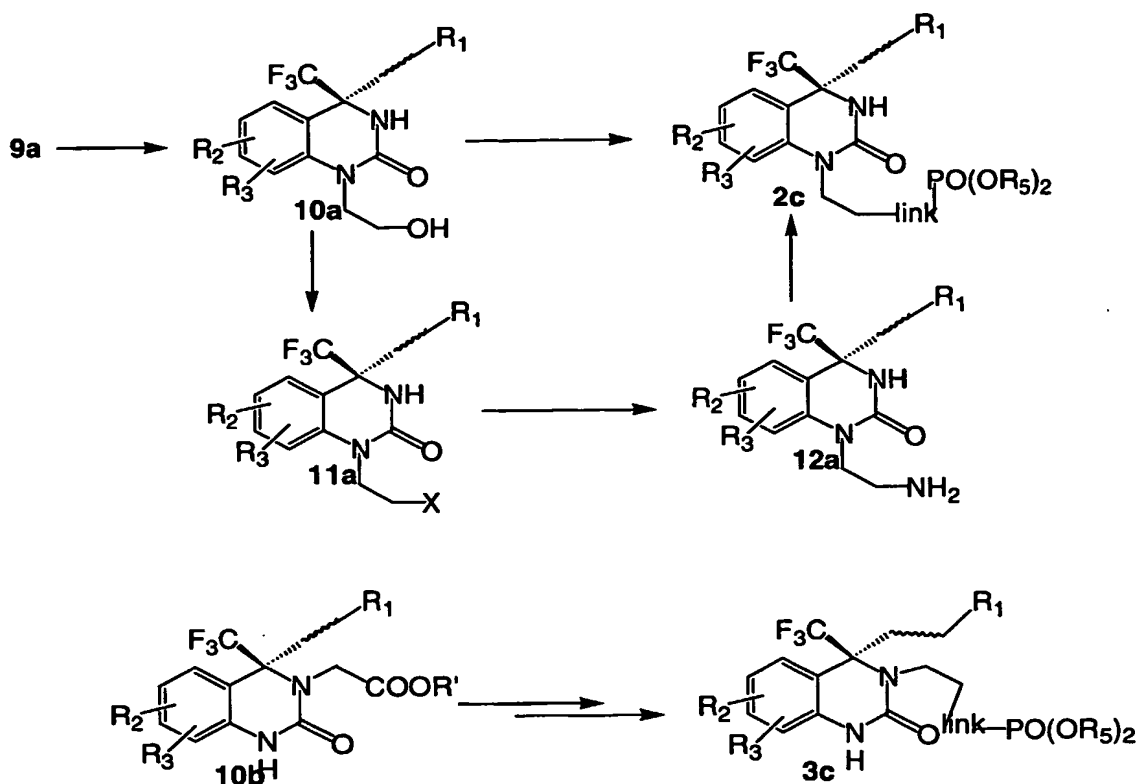
Scheme 2

Scheme 3

Scheme 4 shows the preparation of quinazolinone-phosphonate conjugates type **4** in

5   Figure 2. Substituted aniline **6** with a functional group Z, which is bearing a protected alcohol
or amino group, or protected alcohol or amino alkyl, is converted to trifluoromethyl phenyl
ketone **13**, which is subsequently converted to quinozolinone **14a**, following the procedure
described in US Patent No. 6423718. Deprotection of the protecting group, followed by
reacting with reagents **8** under suitable conditions give the desired the phosphonate **4a**.

10 Quinazoline **14b**, prepared according to US Patent No. 6423718, is converted to phosphonate
4b by reacting with phosphonate reagent **8** directly (R_3=NH_2), or after deprotection
(R_3=OMe) under the condition such as for example, BCl_3, many examples are described in
Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons
Inc. Synthesis of compound **6** is described in Scheme 5.

15

Scheme 4

R3 = OMe, NH2
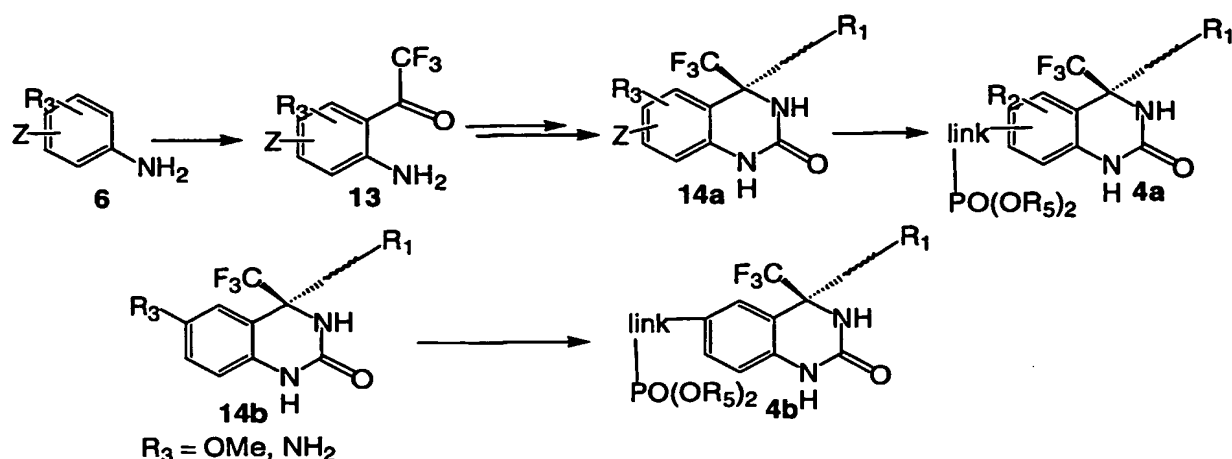
Scheme 5 shows compounds **6** are obtained through modification of commercial available material 2-halo-5-nitroaniline, or 5-halo-2-nitroaniline (**6.0a**). The amino group of **6.0a** is first protected with a suitable protecting group, for example trityl, Cbz, or Boc etc as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Reduction of the nitro group of **6.1a** with a reducing agent, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed, gives **6.1b**, which is then used in the transformation described in Scheme 4.

The amino group of **6.0a** is converted to hydroxyl group to give **6.2a** by established procedures, for example, diazotization followed by treatment with H_2O/H_2SO4, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. The hydroxyl group is then protected with a suitable protecting group, for example trityl ethers, silyl ethers, methoxy methyl ethers etc as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. The nitro group of the resulting compound is then reduced with the above mentioned methods to give **6.2b**, which is then used in the transformation described in Scheme 4.

The hydroxyl or amino alkyls are obtained using the following methods. The amino group of **6.0a** is converted to nitrile **6.3a** with the known method, for example diazotization followed by treatment with cuprous cyanide, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. The nitrile group is then selectively reduced with a reducing agent, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed, to give amine **6.3b**. With the mentioned methods above, the amino group is protected and nitro group is reduced respectively to give **6.3c**. Alternatively, the nitrile **6.3a** is converted to acid **6.4a** and the acid

is subsequently reduced to alcohol to give **6.4b** using the examples described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. Similarly, protection of hydroxyl group followed by reduction of nitro to amine gives **6.4c**. Compound **6.3c** and **6.4c** are used in Scheme 4 respectively.

5   The homologated hydroxyl or amino alkyls are obtained using the following methods (Scheme 3). The acid **6.4a** are extended to acid **6.5a**, which is transformed to nitrile **6.5b**, these two transformation are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed, Nitrile **6.5b** is converted to aniline **6.5c** using the similar methods described above. Alternatively, nitrile **6.5b** is obtained by first convert benzyl

10   alcohol **6.4b** to benzyl halide, then treated with CN- nucleophile. Reduction of acid **6.5a** provided alcohol **6.6b**, which is protected using the protecting groups described above to give the required aniline **6.6c**. Compound **6.5c** and **6.6c** are used in Scheme 4 respectively.

For example aniline **6.0a** (Example 2) is treated with $NaNO_2$ in the presence of acid at 0°C, then the resulting mixture was heated in H_2O to give phenol **6.2a**. The hydroxyl group is

15   then protected as methoxyl methyl ether by treating phenol **6.2a** with MOMCl in the presence of Hunig's base to yield **6.21b**. Hydrogenation of nitrobenzene affords aniline **6a**. Aniline **6a** is converted to phenyl trifluoromethyl ketone **13a.1**, which is subsequently transformed to quinazolinone analog **14a.1**, using the method described in US Patent No. 6423718. Deprotection of the MOM-ether with trifluoroacidic acid provides phenol **15**. Treatment of

20   **15**, in acetonitrile, with triflate methyl phosphonic acid dibenzyl ester **8.2** in the presence of Cs_2CO_3 gives **4a.1**. Alternatively, reaction of phenol **15** with ethylenediol under the Mitsunobu condition produces **16**. Hydroxyl group of **16** as activated as carbamate, subsequent treatment with amino methyl phosphonate **8.3** affords phosphonate analog **4a.2**.

Example 3 shows 2-chloro-5-nitro aniline **6.0b** transformed to nitrile **6.31a** by reacting

25   with $NaNO_2$ and then CuCN subsequently. Hydrolysis of nitrile **6.31a** gives acid **6.41a**. Treatment of **6.41a** with ClCOOEt in the presence of base at 0°C followed by CH_2N_2 provides diazoketone, which is converted to methyl ester **6.51a** upon treating with silver perchlorate in methanol. The ester group is then reduced to give alcohol, which is protected as MOM-ether to provide **6.61c**. The nitro group is then reduced to amine to afford **6b**. Aniline **6b** is

30   converted to quinazolinone analog **14** using the method described in US Patent No. 6423718. Deprotection of the MOM-ether with trifluoroacidic acid provide alcohol **16**. The aldehyde **17** is obtained by oxidation of alcohol. Reductive amination of **17** with amino ethyl phosphonate **8.4** afford analog **4a.3**.
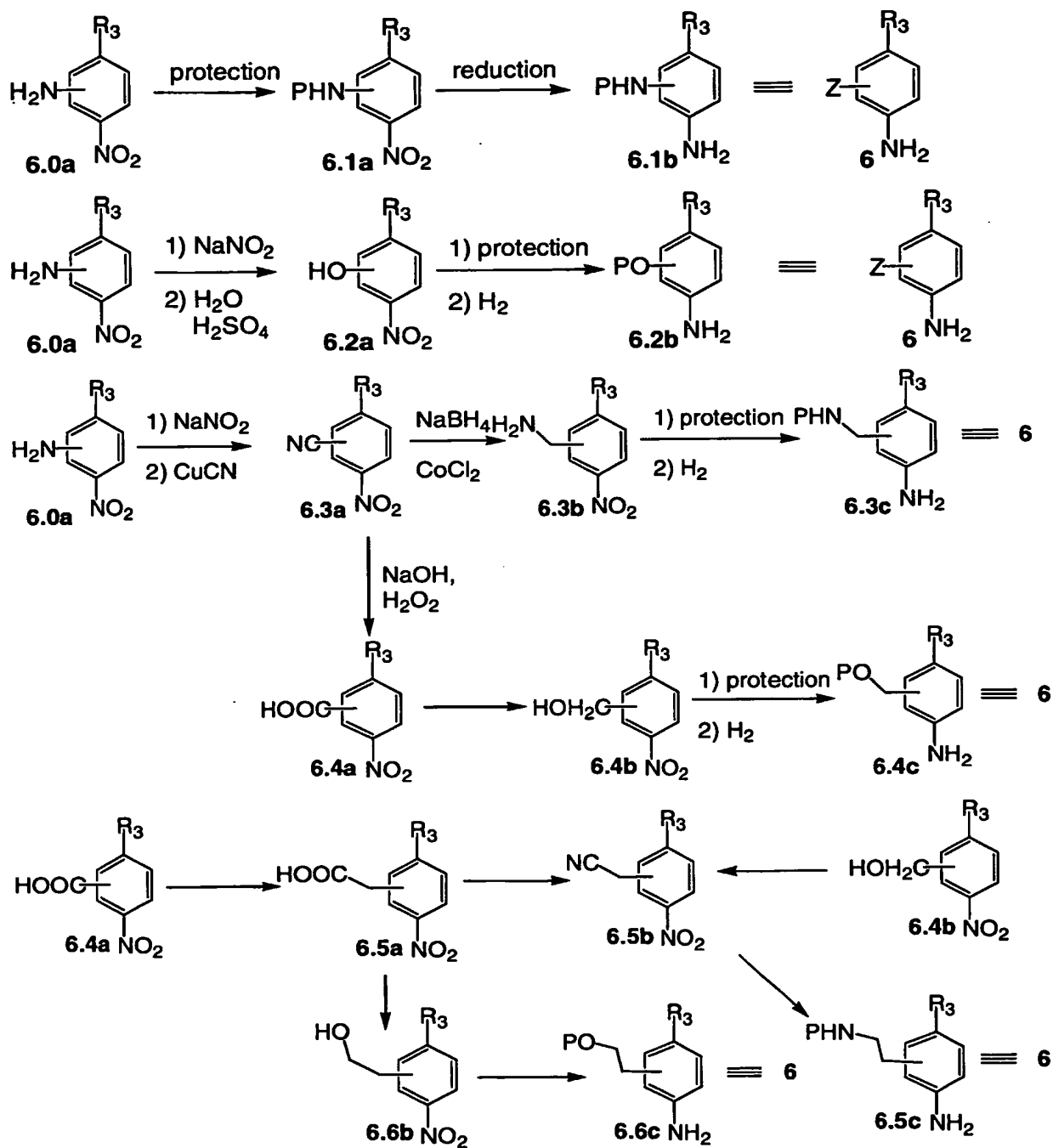
Scheme 5
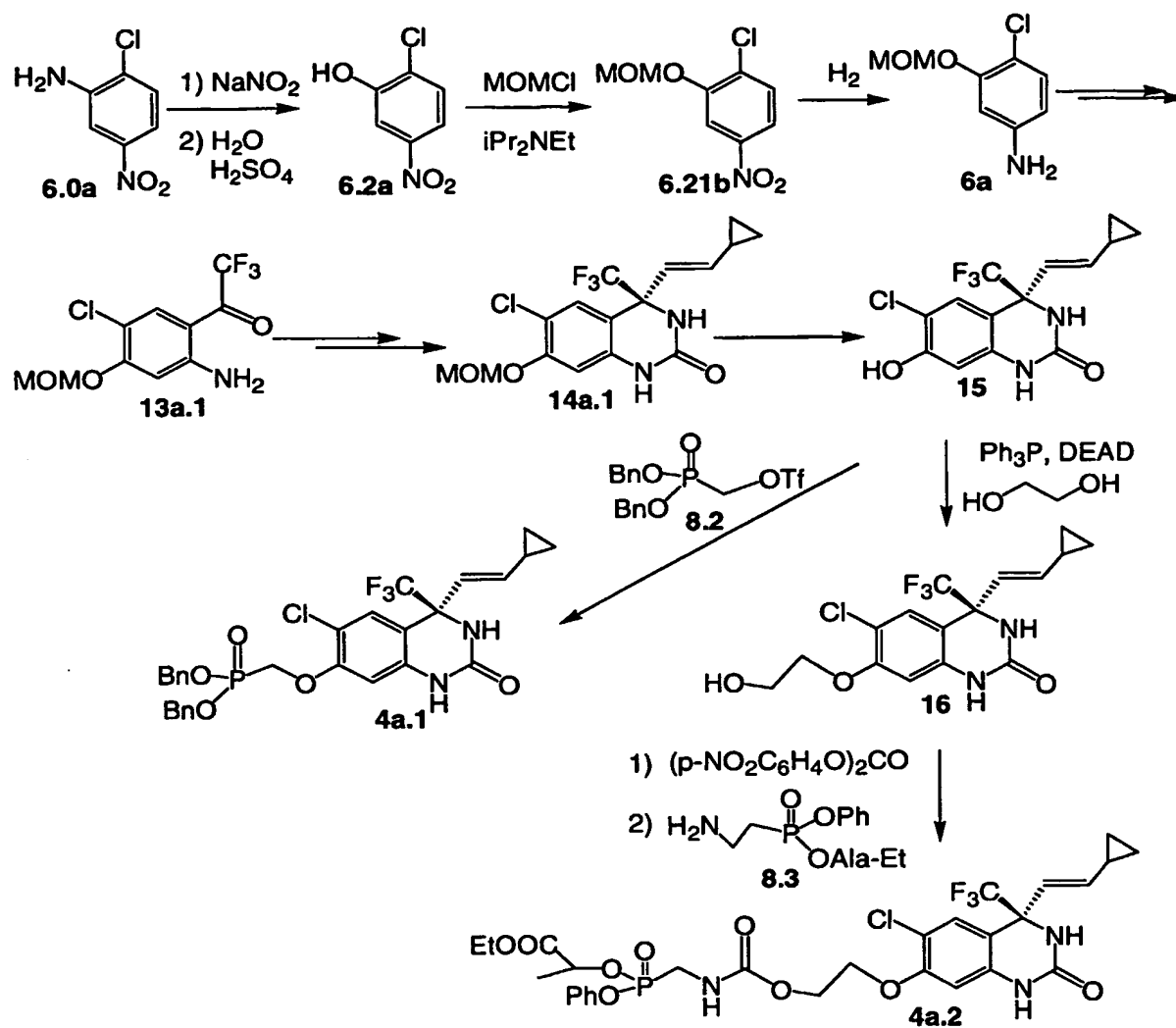
<u>Example 2</u>

Example 3

5
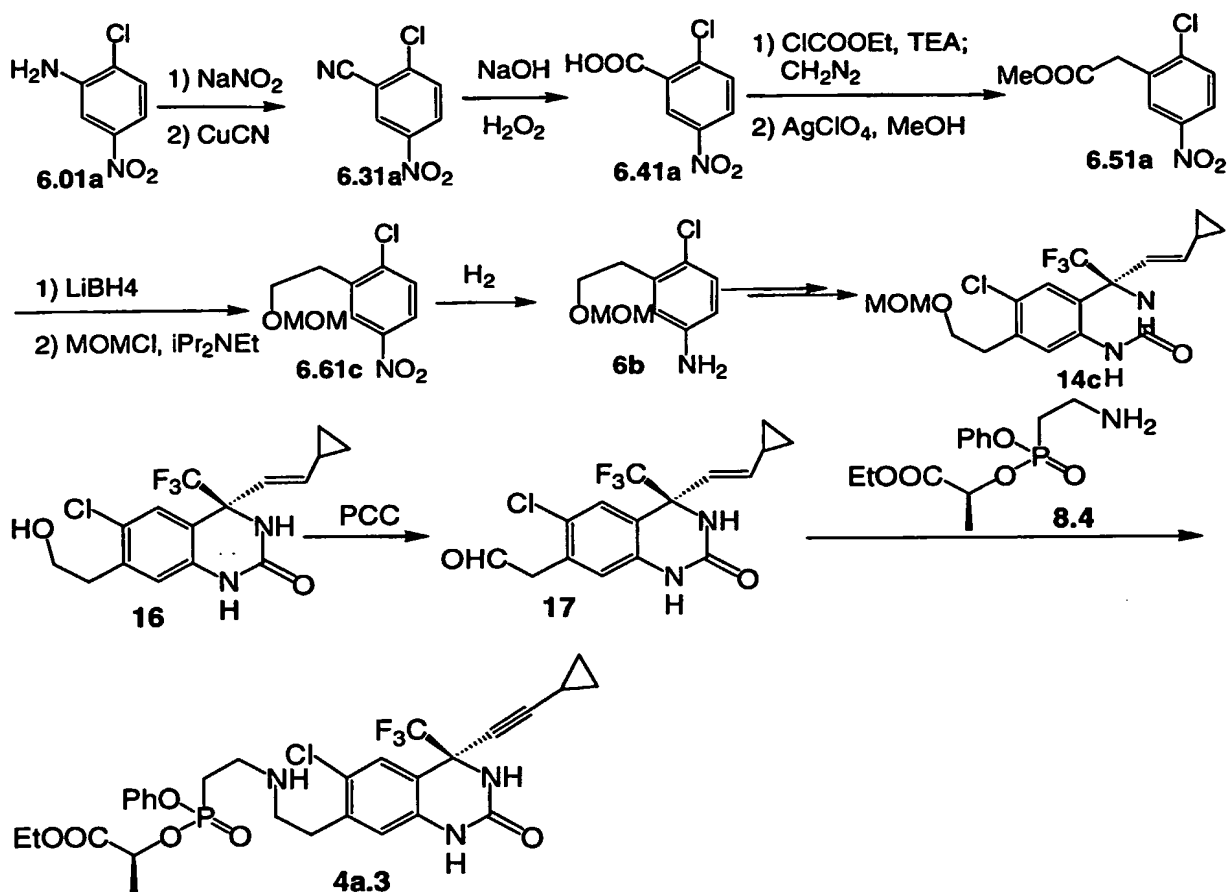
Preparation of phosphonate analog type **5** from quinazolinone **1** is outlined in Scheme 6. Quinazolinone **1**, which R$_1$ contains OH, or NH$_2$ or NHR$_1$' as the attachment site for connecting phosphonate, reacts with reagent **8** under suitable conditions to provide phosphonate analog **5**. For example (Example 4), Quinozalinone **1b.1**, obtained as described

10   in US Patent No. 6423718, is treated with phosphonate reagents **8.2** in the presence of Cs$_2$CO$_3$, give phosphonate **5a**.

Scheme 3
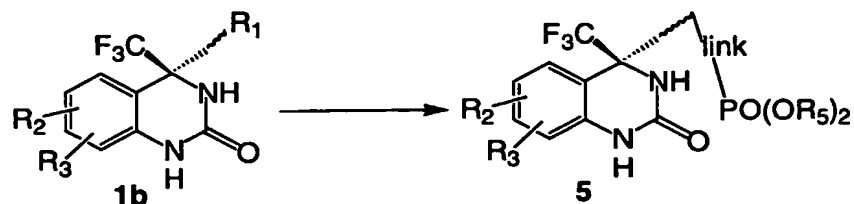
R$_1$: defined as above but contains OH, NH$_2$

15

Example 4
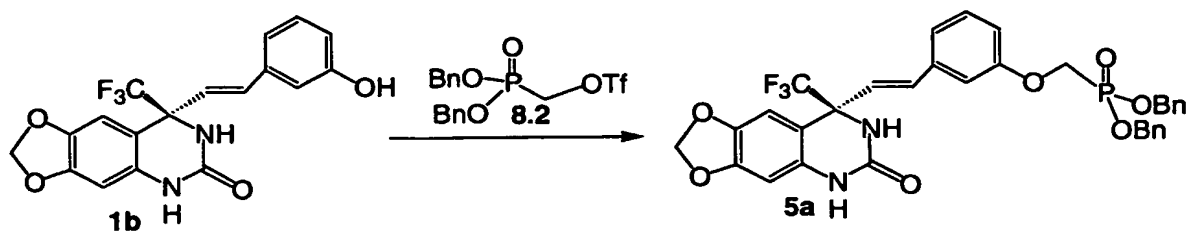
Efavirenz-like phosphonate NNRTI compounds

5   The present invention includes efavirenz-like phosphonate NNRTI compounds and

methods for the preparation of efavirenz phosphonate analogs shown in Figure 1.

link = linkage group
R = OAr, O-heteroaryl, amino acid ester
    substituted OAr, O-heteroaryl
R1 = amino acid ester,
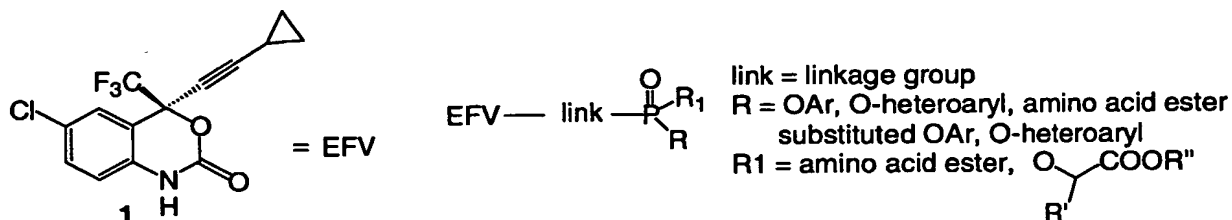
Figure 1.

10   A link group includes a portion of the structure that links two substructures, one of

which is efavirenz having the general formula shown above, the other is a phosphonate group

bearing the appropriate R and R₁ groups. The link has at least one uninterrupted chain of

atoms other than hydrogen.

           Efavirenz and its analogs have demonstrated therapeutic acitivity against HIV

15   replication, and efavirenz is currently used in clinical for treatment of HIV infection and AIDS.

The present invention provides novel analogs of efavirenz. Such novel efavirenz analogs

possess all the utilities of efavirenz and optionally provide cellular accumulation as set forth

below.

           The intermediate phosphonate esters required for conversion into the prodrug

20   phosphonate moieties bearing amino acid, or lactate esters are shown in Figure 2.
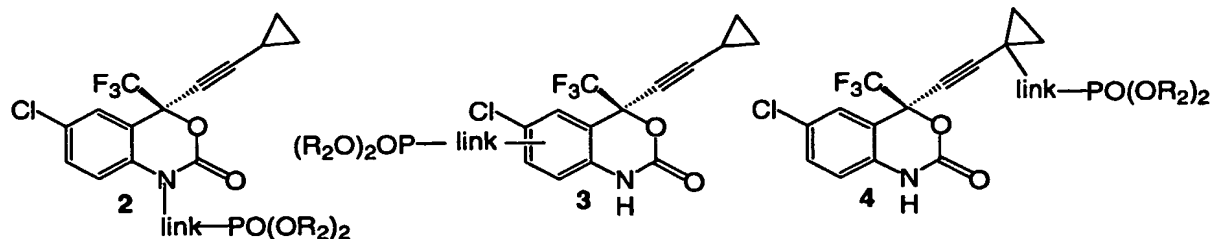
Figure 2

Compound **1** can be synthesized as described in US Patent No. 5519021. Preparation of compound **2** from efavirenz **1** is outlined in Scheme 1. Efavirenz **1** is dissolved in suitable solvent such as, for example, DMF or other protic solvent, and treated with the phosphonate

5 reagent **5** in the presence of a suitable organic or inorganic base. For example, **1** is dissolved in DMF, is treated with sodium hydride and 1 equivalent of triflate methyl phosphonic acid dibenzyl ester **5.1** prepared to give EFV phosphonate **2** in which the linkage is a methylene group. Using the above procedure but employing different phosphonate reagents **5** in place of **5.1**, the corresponding products **2** are obtained bearing different linking group.

10 Scheme 1.
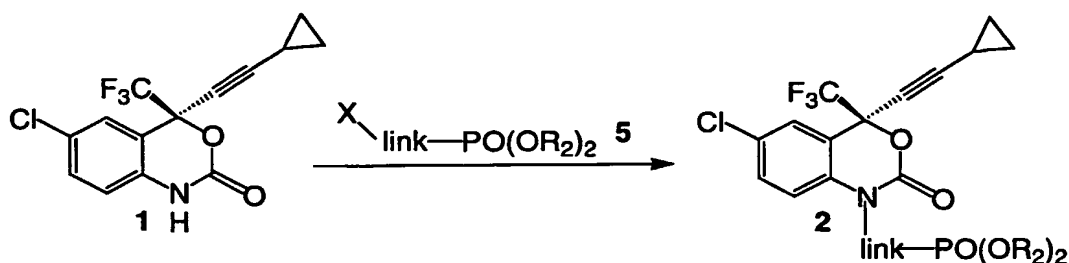
Example 1
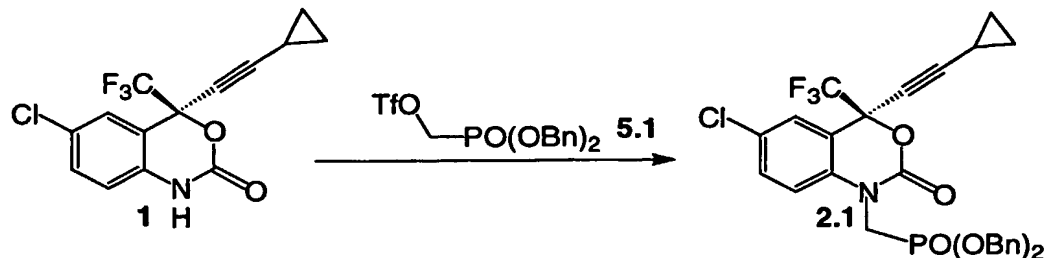
Scheme 2 shows the preparation of EFV-phosphonate conjugates compounds **3** in

15 Figure 2. *p*-Chloro aniline with functional group Z, which bears a protected alcohol or amino group, or protected alcohol or amino alkyl, is converted to compound **7** following the procedure described in US Patent No. 5519021. Deprotection of the protecting group, followed by reacting with reagent **5** in the above mentioned conditions give the desired the compound **3**. As shown in Scheme 3, compounds **6** are obtained through modification of

20 commercial available material 2-chloro-5-nitroaniline, or 5-chloro-2-nitroaniline (**6.0a**).
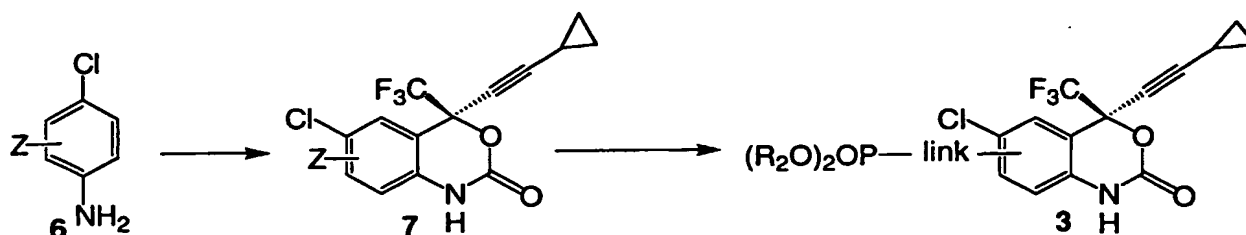
Scheme 2

The amino group of **6.0a** is first protected with a suitable protecting group (Scheme 3), for example trityl, Cbz, or Boc etc as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Reduction of the nitro group in **6.1a** with a reducing agent, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed, give **6.1b**, which is then used in the transformation described in Scheme 2.

Alternatively, the amino group of **6.0a** is converted to hydroxyl group to give **6.2a** by established procedures, for example, diazotization followed by treatment with H_2O/H_2SO_4, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. The hydroxyl group is then protected with a suitable protecting group, for example trityl ethers, silyl ethers, methoxy methyl ethers etc as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. The nitro group of the resulting compound is then reduced with the above mentioned methods to give **6.2b**, which is then used in the transformation described in Scheme 2.

The hydroxyl or amino alkyls are obtained using the following methods. The amino group in **6.0a** is converted to nitrile **6.3a** with the known method, for example diazotization followed by treatment with cuprous cyanide, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. The nitrile group is then selectively reduced with a reducing agent, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed, to give amine **6.3b**. With the mentioned methods above, the amino group is protected and nitro group is reduced respectively to give **6.3c**. In addition, the nitrile **6.3a** is converted to acid **6.4a** and the acid is subsequently reduced to alcohol to give **6.4b**, and the reduction of nitro to amine give **6.4c**, using the methods described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. Both **6.3c** and **6.4c** used in the transformation described in Scheme 2. The homologated hydroxyl or amino alkyls are obtained using the following methods (Scheme 3). The acid **6.4a** are extended to acid **6.5a**, which is transformed to nitrile **6.5b**, these two transformation are described in R. C. Larock, Comprehensive Organic Transformation, John

Wiley & Sons, 2nd Ed, Nitrile **6.5b** is converted to aniline **6.5c** using the similar methods described above. Alternatively, nitrile **6.5b** is obtained by first convert benzyl alcohol **6.4b** to benzyl halide, then treated with CN- nucleophile. Reduction of acid **6.5a** provided alcohol **6.6b**, which is protected using the protecting groups described above to give the required

5   aniline **6.6c**. Both **6.5c** and **6.6c** used in the transformation described in Scheme 2.

For example aniline **6.0a** (Example 2) is treated with NaNO$_2$ in the presence of acid at 0°C, then the resulting mixture was heated in H$_2$O to give phenol **6.2a**. The hydroxyl group is then protected as methoxyl methyl ether by treating phenol **6.2a** with MOMCl in the presence of Hunig's base to yield **6.21b**. Hydrogenation of nitrobenzene affords aniline **6.2a**. Aniline

10   **6a** is converted to efavirenz analog **7.1**. Deprotection of the MOM-ether with trifluoroacidic acid provides phenol **8**. Treatment of **8** in acetonitrile with (trifluorosulfonylmethyl)-phosphonic acid dibenzyl ester **5.1** in the presence of Cs$_2$CO$_3$ gives **3a**.

In Example 3, 2-chloro-5-nitro aniline **6.0b** is transformed to nitrile **6.31a** by reacting with NaNO$_2$ and then CuCN subsequently. Hydrolysis of nitrile **6.31a** gives acid **6.41a**.

15   Treatment of **6.41a** with ClCOOEt in the presence of base at 0°C followed by CH$_2$N$_2$ provides diazoketone, which is converted to methyl ester **6.51a** upon treating with silver perchlorate in methanol. The ester group is then reduced to give alcohol, which is protected as MOM-ether to provide **6.61c**. The nitro group is then reduced to amine to afford **6b**. Aniline **6a** is converted to efavirenz analog **7.1**. Deprotection of the MOM-ether with trifluoroacetic acid

20   provides phenol **9**. The aldehyde **10** is obtained by oxidation of alcohol. Reductive amination of **10** with agent **5.2** affords analog **3b**.

Scheme 3
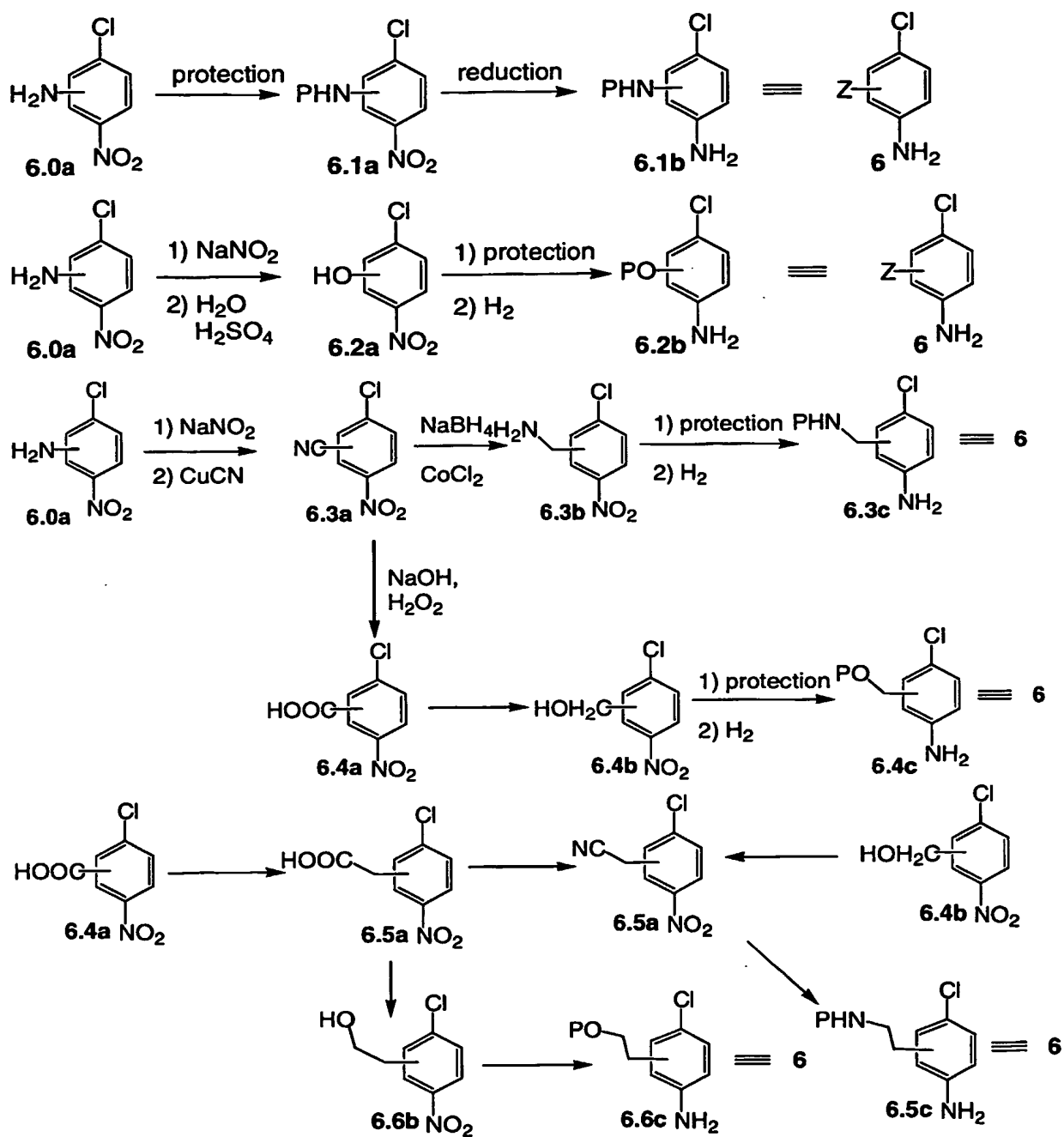
Example 2
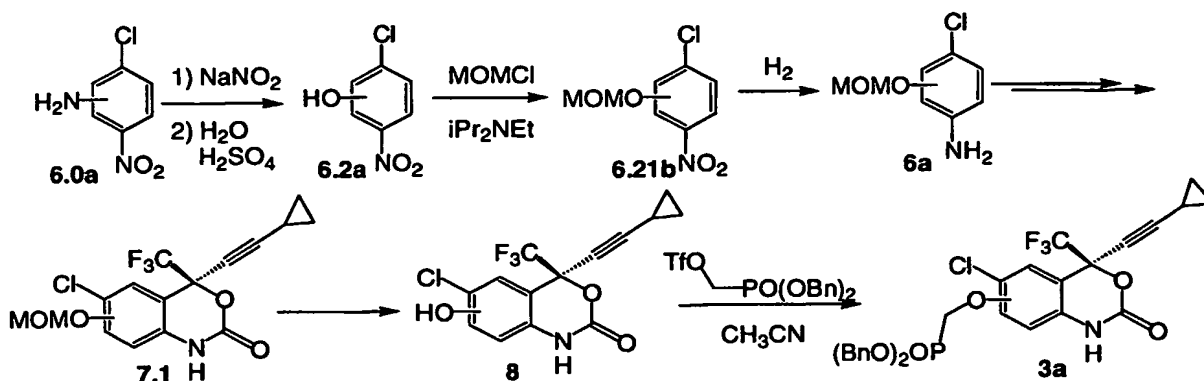
5   Example 3
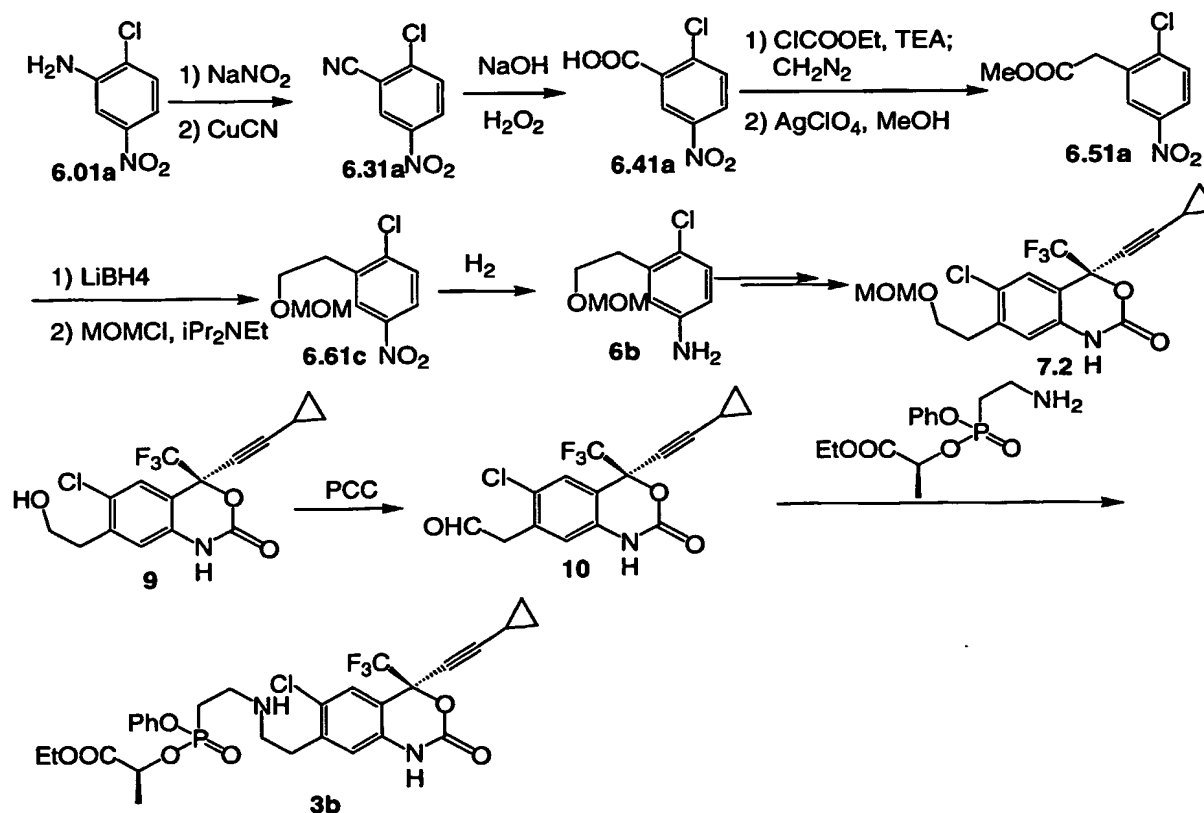
Preparation of compound **2** from efavirenz **1** is outlined in Scheme 4. Compound **12**, obtained as described in US Patent No. 5519021, reacting with Grignard reagent, generated
10   from protected acetylene **11** following the procedure described in US Patent No. 5519021, gives compound **13a**. The hydroxyl group in **11** is protected as its silyl ether, trityl ether etc. Removal of the protecting group of **13a** yields alcohol **14a**. Alkylation of **14a** with agent **5** affords phosphonate **4.1**. Alternatively, compound **15**, obtained as described in US Patent No.

5519021, reacts with aldehyde or ketone to give alcohol **14b**, which is converted to analog **4b** using the conditions described above. Amine **14c** is obtained from alcohol **14b** under the standard conditions. Amine **14c** is converted to phosphonate **4c** either by reacting with agent **5** or reductive amination with a phosphonate reagents containing an aldehyde group. For example, treatment of compound **14** with n-BuLi followed by paraformaldehyde gives alcohol **14b.1**. Treatment of alcohol **14b.1** with Mg(OtBu)₂ followed by phosphonate provides phosphonate **4.2b**.

Scheme 4
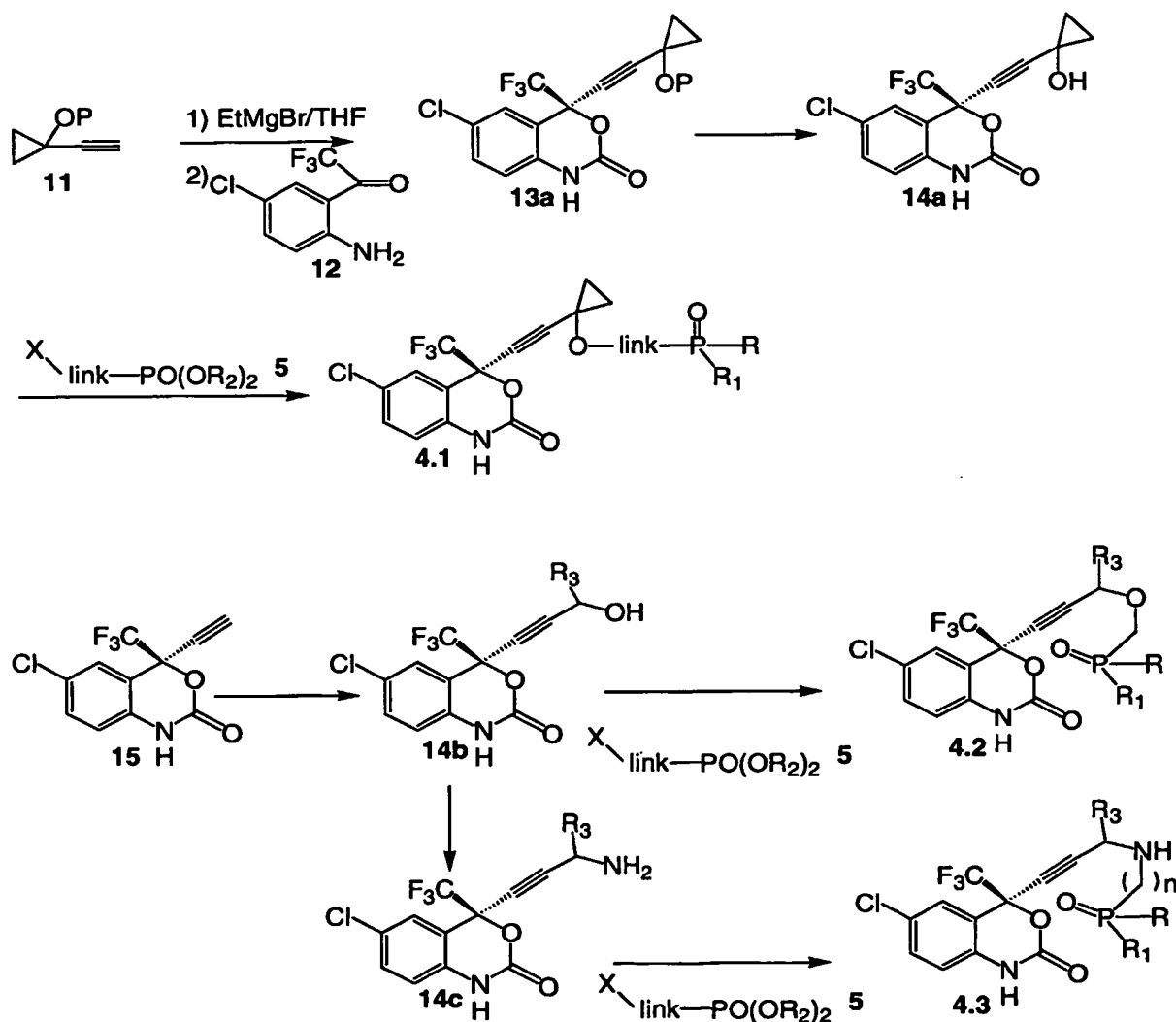
Example 4
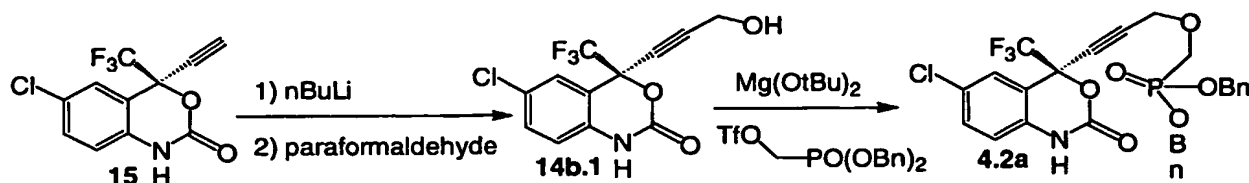
Benzophenone-like phosphonate NNRTI compounds

The present invention describes methods for the preparation of phosphonate analogs of benzophenone class of HIV inhibiting pyrimidines shown in Figure 1 that are potential anti-HIV agents.
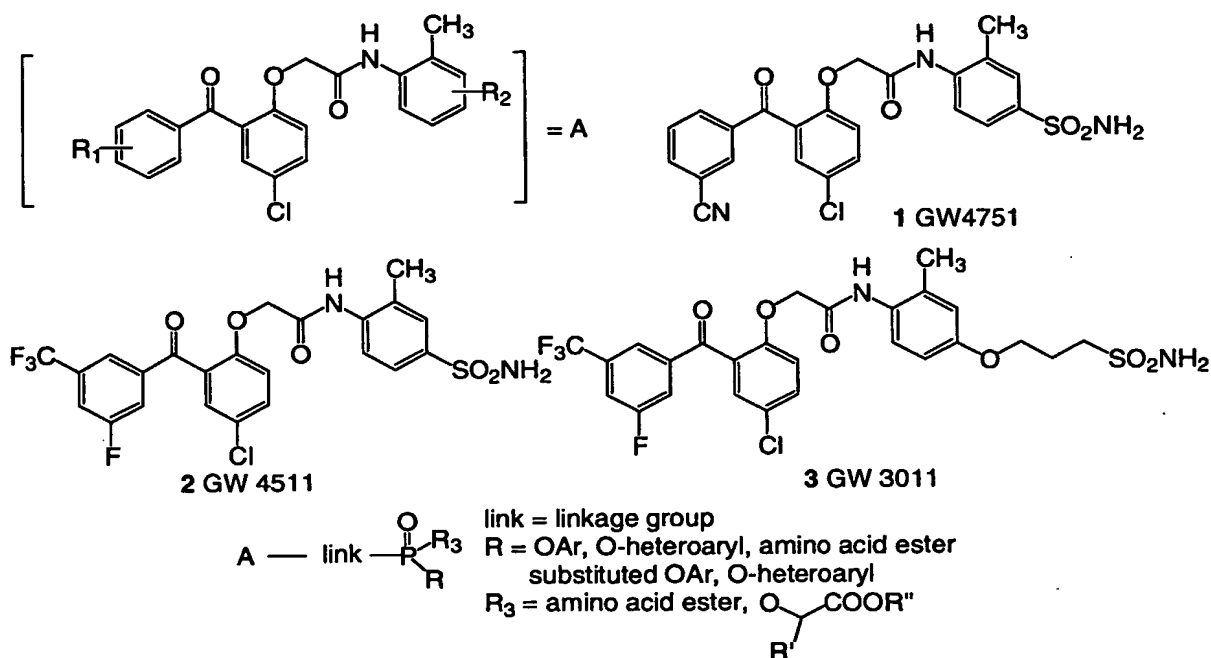
R_1 = halide, CF_3, CN, NO_2, C_{1-6} alkyl, OR^1, NHR^1, NHR^1R^2, where R^1 and R^2 are C_{1-6} alkyl

R_2 = OH, OR^1, NHR^1, NHR^1R^2, SO_2NH_2, SO_2NHR^1, $SONR^1R^2$, $CONH_2$, $CONHR^1$, OR^3 where R^3 is H or R_1

Figure 1

A link group includes a portion of the structure that links two substructures, one of which is benzophenone class of HIV inhibiting agents having the general formula shown

above, the other is a phosphonate group bearing the appropriate R and R_3 groups. The link

has at least one uninterrupted chain of atoms other than hydrogen.

Benzophenone class of compounds has shown to be inhibitors of HIV RT. The

present invention provides novel analogs of benzophenone class of compound. Such novel

5   benzophenone analogs possess all the utilities of benzophenone and optionally provide cellular

accumulation as set forth below.

The intermediate phosphonate esters required for conversion into the prodrug

phosphonate moieties bearing amino acid, or lactate esters are shown in Figure 2.

10
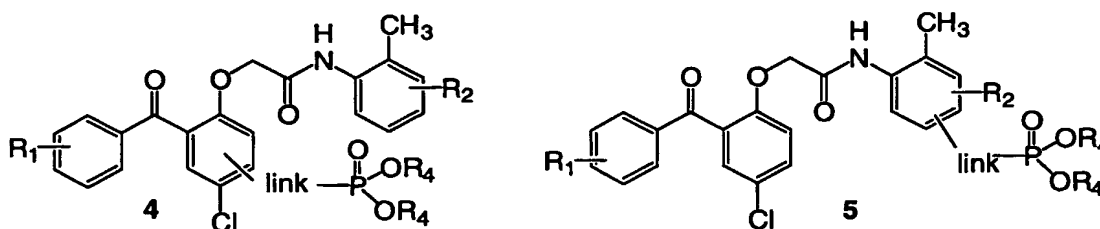
Figure 2

Preparation of phosphonate analog 4 is outlined in Scheme 1. Benzophenone 8 is

obtained from Freidel-Crafts reaction of substituted benzoyl chloride 7 and 4-chloro-phenol

15   methyl ether which bearing a protected amine or hydroxyl group Z. Phenol ether is obtained

by selective protection of commercially available 4-chlorophenol substituted with amino- or

hydroxyl group. Benzoyl chloride is obtained either from commercial sources or prepared

from commercial available benzoic acid. Benzophenone 8 is also obtained from oxidation of

the corresponding alcohol, which in turn is obtained from the reaction of benzaldehyde and

20   anion. Removal of methyl provides phenol 9. Alkylation of phenol with bromoacetate such

as ethyl bromoacetate affords ester 10. The ester is then converted to acid. Formation of

amide 12 from acid 11 and aniline 10 is achieved following the standard amide formation

methods, many examples are described in R. C. Larock, Comprehensive Organic

Transformation, John Wiley & Sons, 2nd Ed. Removal of the protecting group of Z followed

25   by reacting with reagent 6 affords phosphonate analog 4a.

For example (Example 1), commercially available 3-cyanobenzoyl chloride is treated

with trichloroaluminum followed by 3,4-dimethoxy chlorobenzene to give benzophenone 8a.

Treatment of 8 with BCl_3 removes the methyl to give diphenol, which is selectively protected

as its mono MOM-ether to give 9a. Alkylation of phenol 9a with ethyl bromoacetate gives

ester **10a**. Hydrolysis of the ester affords acid **11a**. Coupling if the acid **11a** with aniline

produces **12a**. The MOM- group is then removed to yield phenol **12b**. Phenol is then

activated as its 4-nitro-phenyl carbonate by reacting with bis(4-nitro-phenyl)carbonate, which

is subsequently treated with aminoethyl phosphonate to give 4a.1.

Alternatively (Scheme 2), amine 10 is transformed to phenol 11 as described in, the hydroxyl

group is then serves as the linking site for a suitable phosphonate group.

Scheme 1
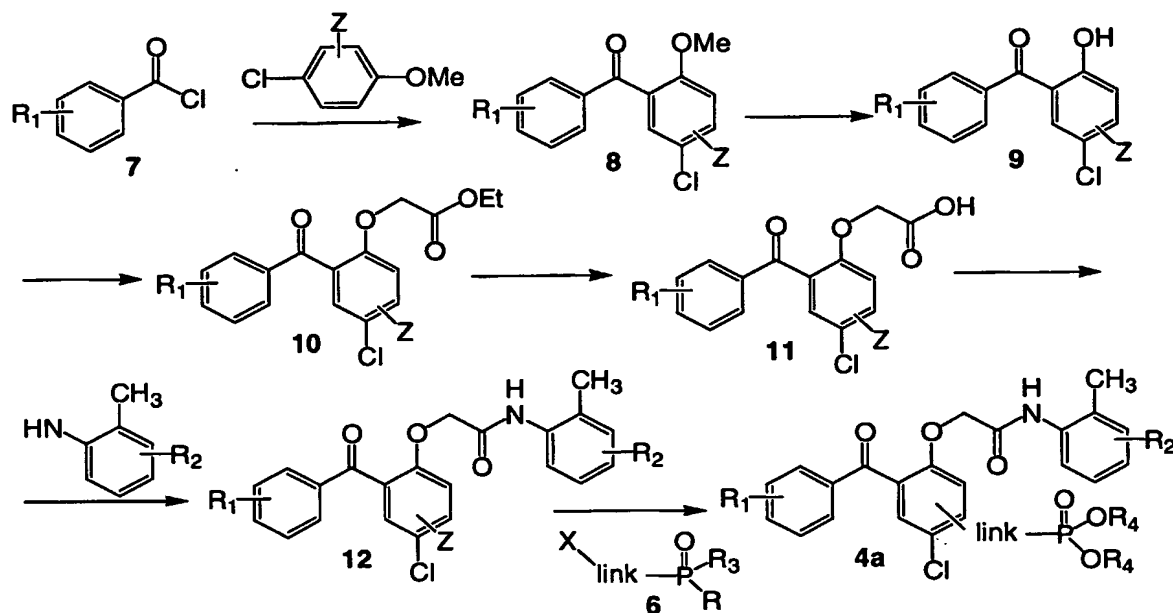
Example 1
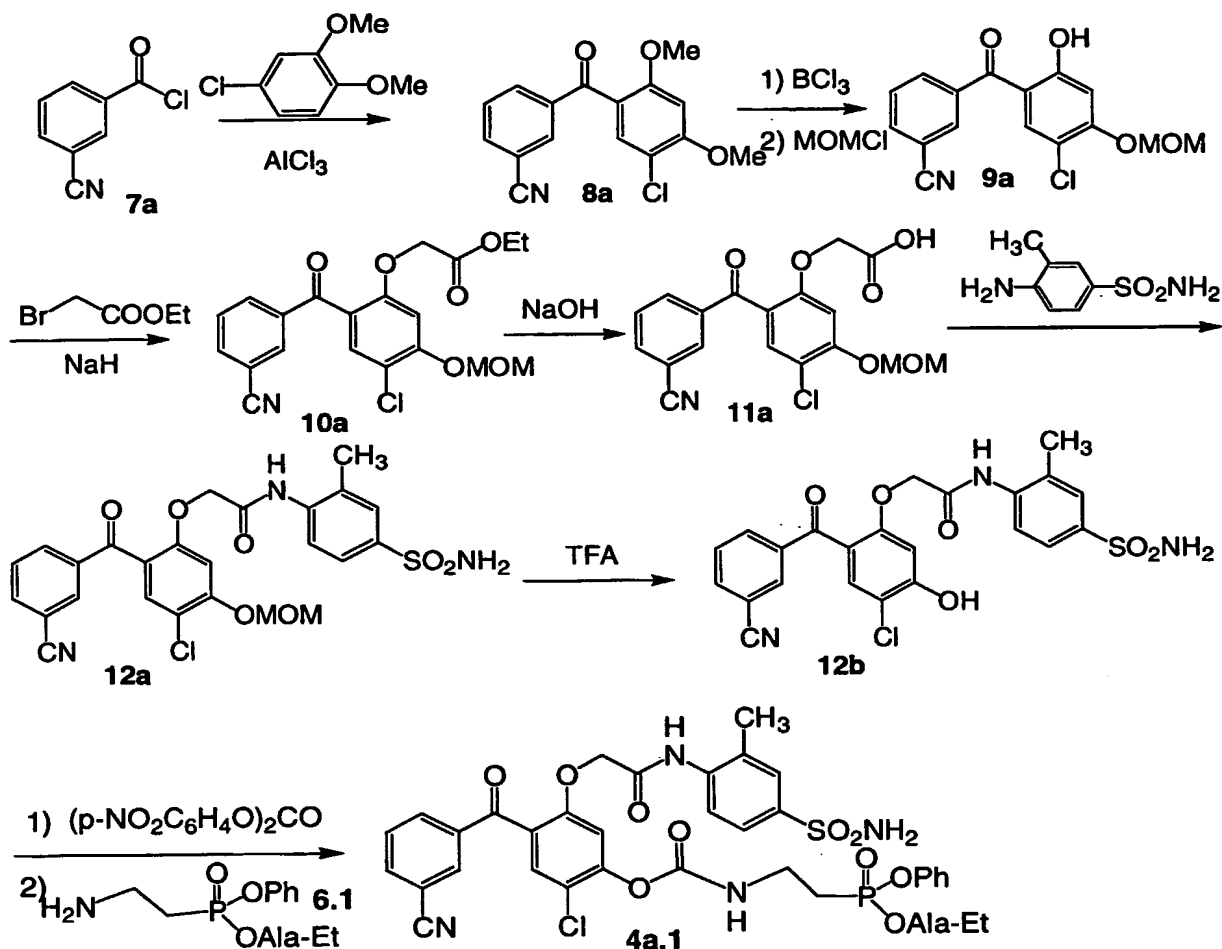
5   Scheme 2 shows the preparation of phosphonate analog type 5. Benzophenone 11b

reacts with aniline 14, bearing a protect hydroxyl or amino group, gives amide 13. Formation

of amide 13 from acid 11b and aniline 14 is achieved following the standard amide formation

methods, many examples are described in R. C. Larock, Comprehensive Organic

Transformation, John Wiley & Sons, 2nd Ed. Removal of the protecting group of Z followed

10   by reacting with reagent 6 affords phosphonate analog 5a. For example (Example 2), acid 11b

couples with aniline 14 provides amide 13a. The MOM-group is then deprotected with TFA

to afford phenol 13b, which is then coupled with hydroxy ethyl phosphonic acid dibenzyl ester

in the presence of Ph3P/DEAD to give phosphonate 5a. Protected aniline 14a is obtained by

treating the commercially available 4-amino-m-cresol with MOMCl in the presence of base,

15   for example Hunig's base.

Scheme 2
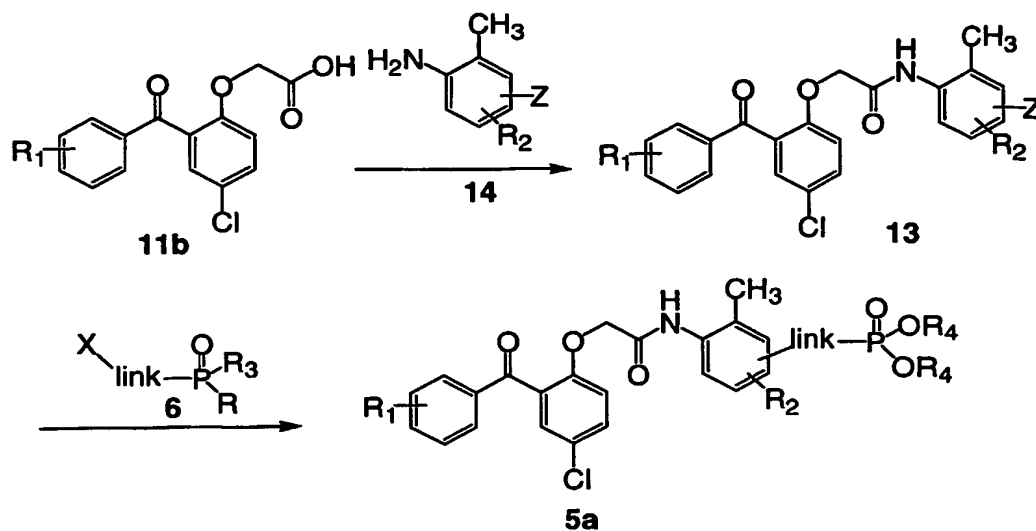
Example 2
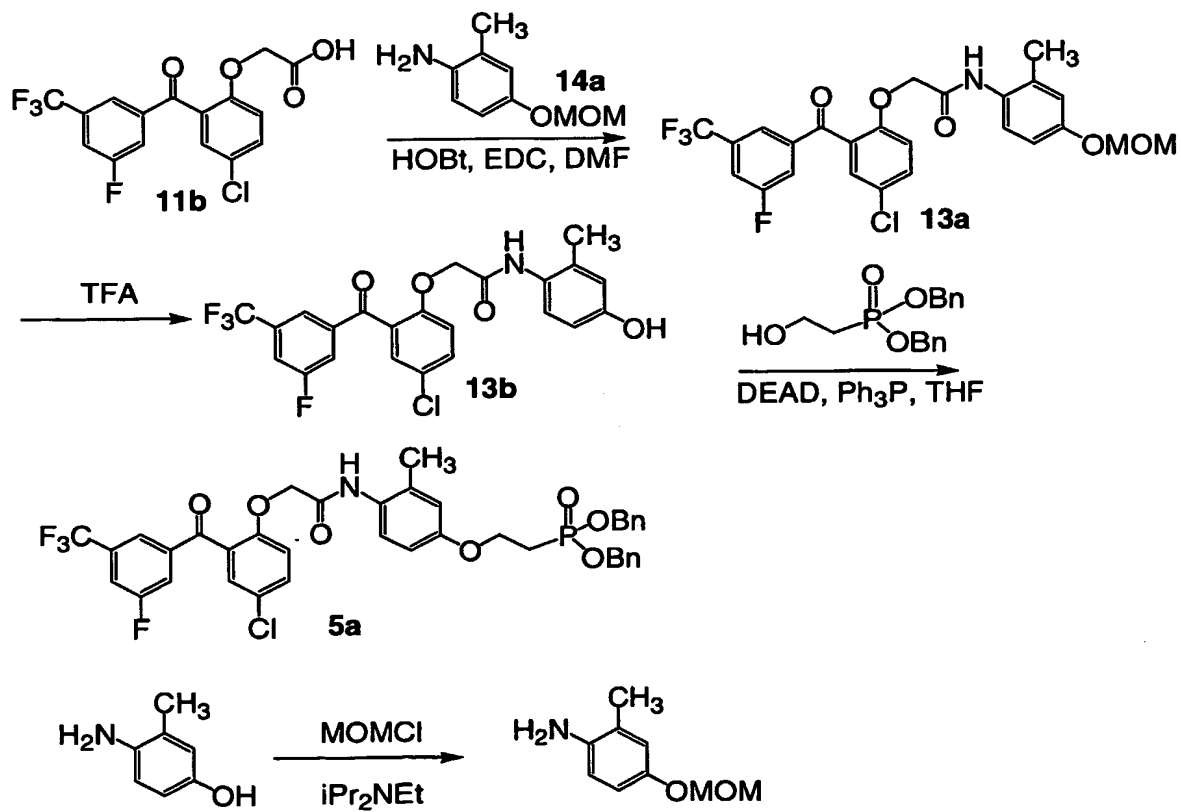
Pyrimidine-like phosphonate NNRTI compounds

The present invention includes Pyrimidine-like phosphonate NNRTI compounds. The present invention also includes methods for the preparation of phosphonate analogs of TMC-125 and TMC-120 class of HIV inhibiting pyrimidines as shown in Figure 1 which are potential anti-HIV agents.

5
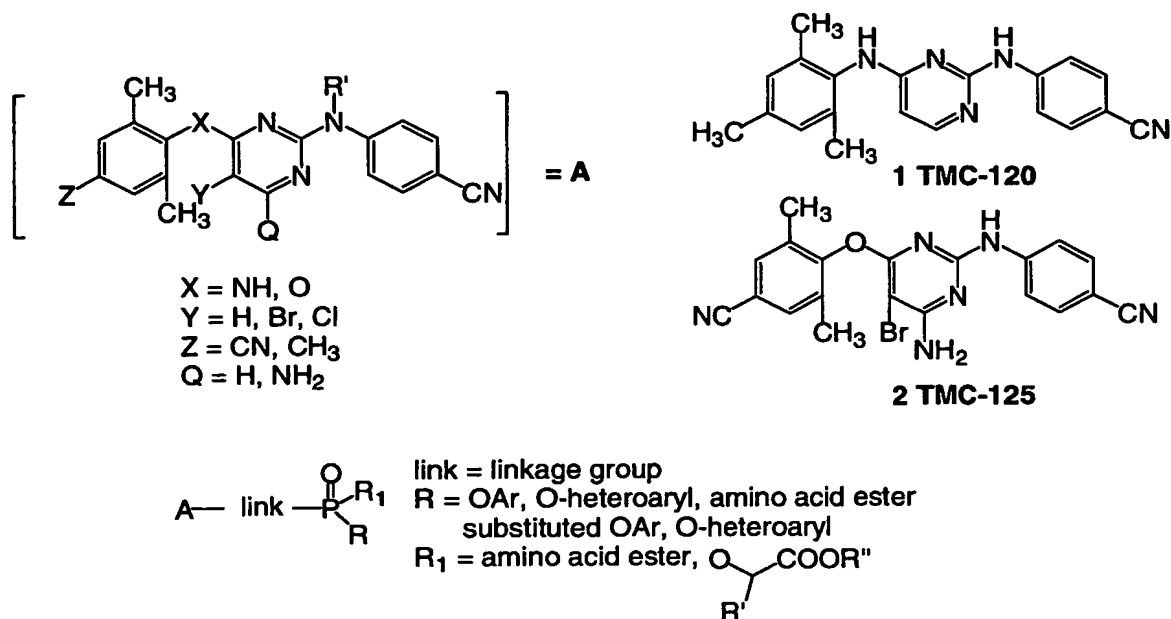
X = NH, O
Y = H, Br, Cl
Z = CN, CH₃
Q = H, NH₂

1 TMC-120

2 TMC-125

link = linkage group
R = OAr, O-heteroaryl, amino acid ester
    substituted OAr, O-heteroaryl
R₁ = amino acid ester, O COOR"

Figure 1

A link group includes a portion of the structure that links two substructures, one of which is TMC-120 and TMC-125 class of pyrimidines having the general formula shown

10   above, the other is a phosphonate group bearing the appropriate R and R1 groups. The link has at least one uninterrupted chain of atoms other than hydrogen.

TMC-125 and TMC-120 class of pyrimidines have demonstrated to be potent in inhibition of HIV replication. Both TMC-125 and TMC-120 are currently in clinical phase II studies for treatment of HIV infection and AIDs. The present invention provides novel

15   analogs of TMC-120 and TMC-125 class of compound. Such novel TMC-120 and TMC-125 class analogs possess all the utilities of TMC-120 and TMC-125 class and optionally provide cellular accumulation as set forth below.

The intermediate phosphonate esters required for conversion into the prodrug phosphonate moieties bearing amino acid, or lactate esters are shown in Figure 2.
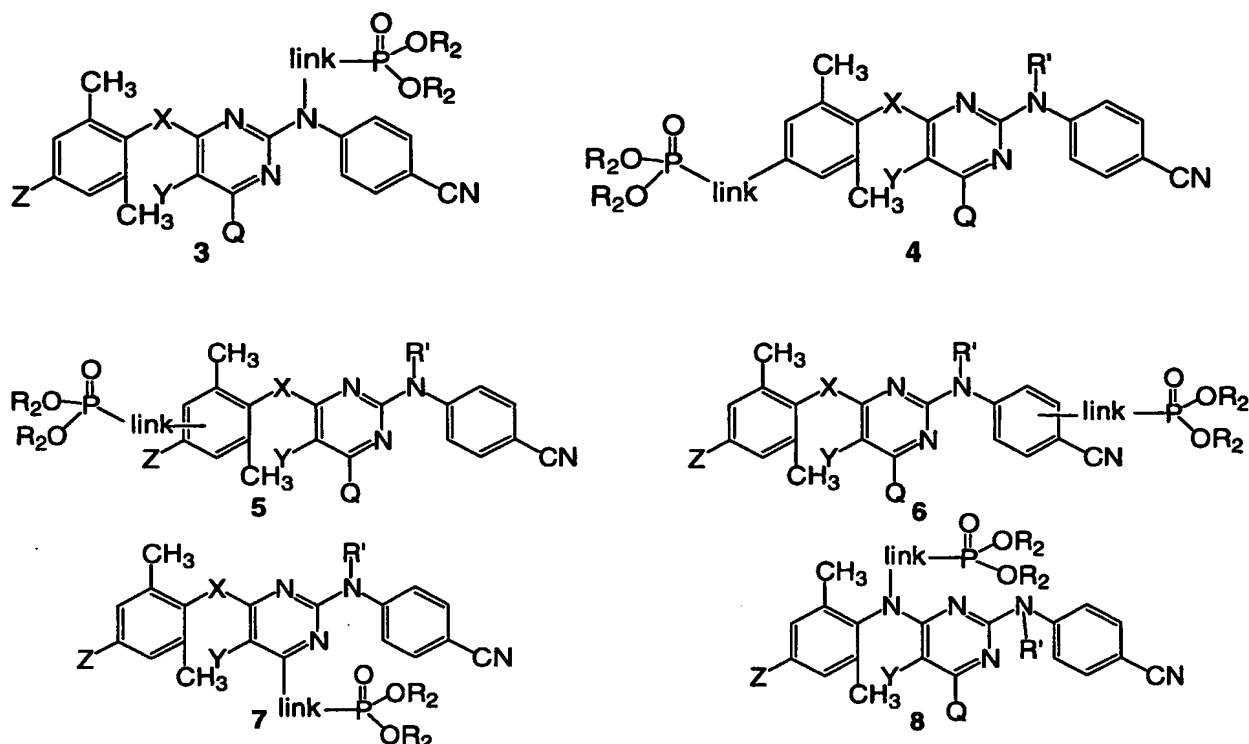
Figure 2

Compounds 1 and 2 can be synthesized as described in US Patent No. 6197779 and WO 0027825. Preparation of phosphonate analog 3 and 7 is outlined in Scheme 1. TMC-125 1 is dissolved in suitable solvent such as, for example, DMF or other protic solvent, and treated with the phosphonate reagent 9, bearing a leaving group, such as, for example,

10   bromine, mesyl, tosyl, or trifluoromethanesulfonyl in the presence of a suitable organic or inorganic base, either 3a or 7a is obtained as the major product depending on the base. For example, 1 was dissolved in DMF, is treated with n-butyl lithium and 1 equivalent of triflate methyl phosphonic acid dibenzyl ester 9.1 prepared to give phosphonate 3a.1 as the major product. Alternatively, treatment of 1 with 9.1 in acetonitrile in the presence of triethylamine

15   provides 7a.1 as the major product. The above procedure provides phosphonate analog 3 in which the linkage is a methylene group. Using the above procedure but employing different phosphonate reagents 9 in place of 9.1, the corresponding products 3 and 7 are obtained bearing different linking group.

Scheme 1

Example 1

5
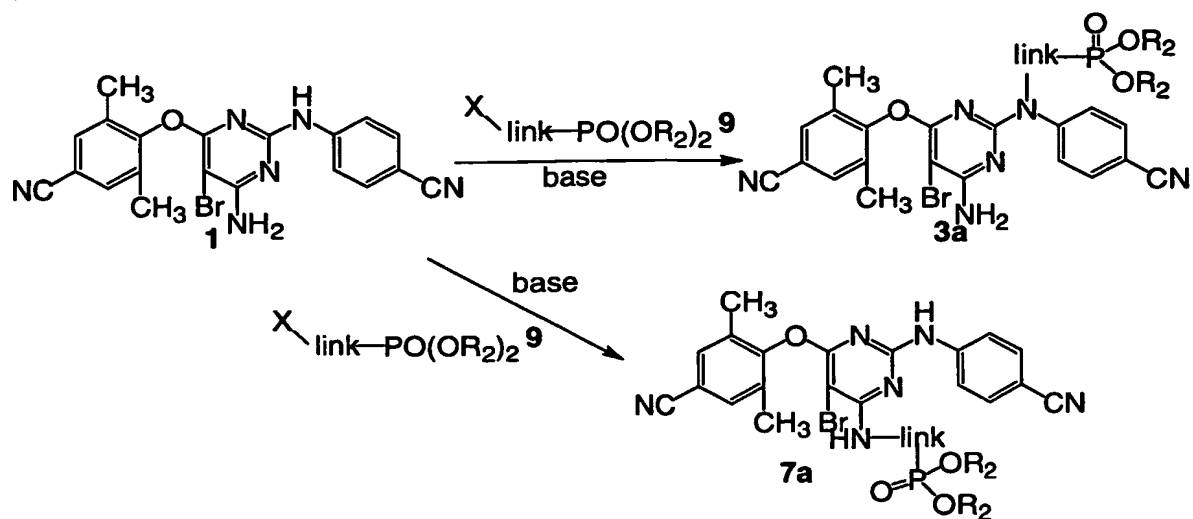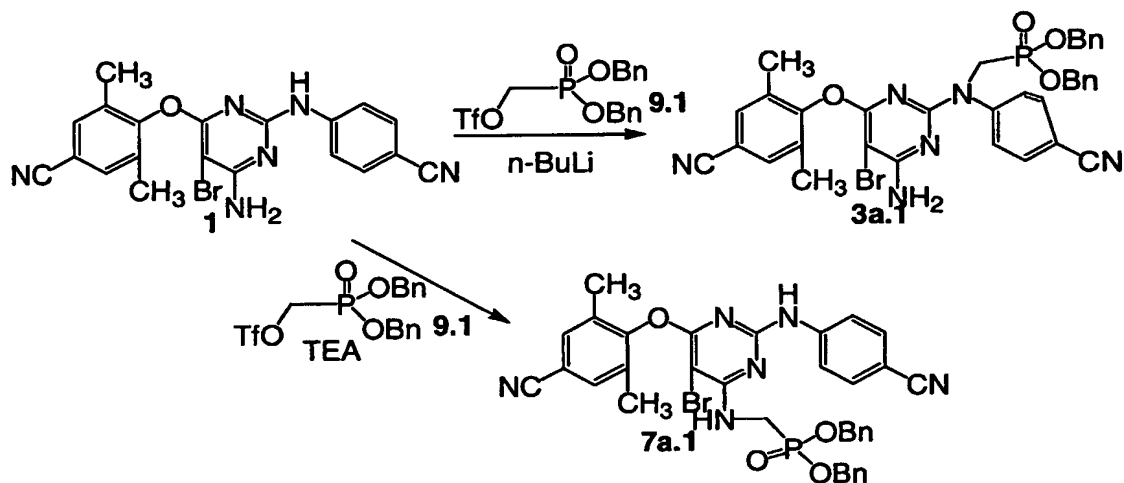
Scheme 2 shows the preparation of phosphonate conjugates compounds type **3** and **8** in Figure 2. TMC-120 **2** is treated with base, and subsequently treated with phosphonate reagent **9** bearing a leaving group, such as, for example, bromine, mesyl, tosyl, or trifluoromethanesulfonyl. The alkylated products are then separated by chromatography. For

10   example (Example 2), treatment of TMC-120 **2** with NaH in DMF, followed by bromomethyl phosphonic acid dibenzyl ester **9.2** gives phosphonate **3b.1** and **8a.1**. The mixture of phosphonates **3b.1** and **8a.1** is separated by chromatography to give pure **3b.1** and **8a.1** respectively.

15   Scheme 2
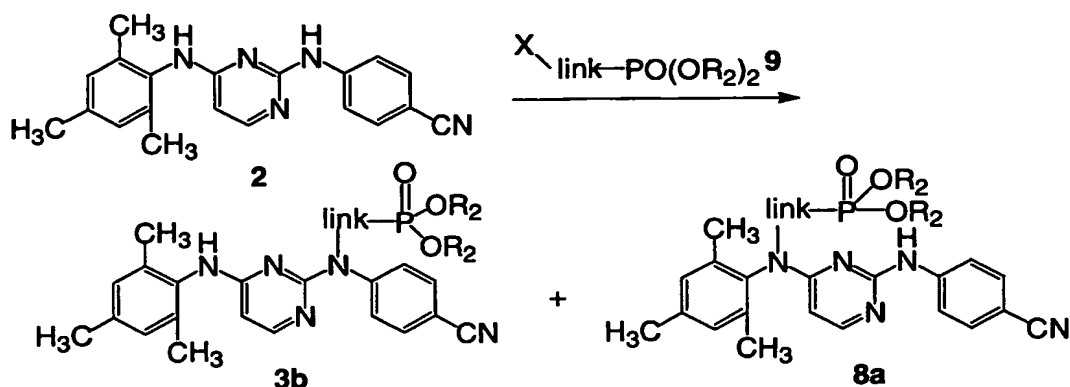
Example 2

5
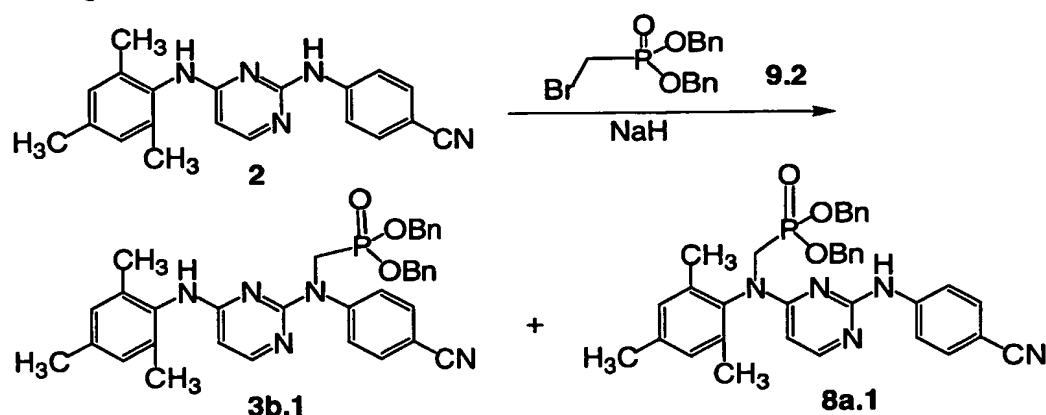
Preparation of phosphonate analogs type **4** in Figure 2 is shown in Scheme 3, 4 and 5. Nitration of commercially available 3,5-dimethyl phenol **10** gives **11**, subsequent reduction of the resulting nitrobenzene **11** provide **12**, many examples are described in R. C. Larock, Comprehensive Organic Transformation, John Wiley & Sons, 2nd Ed. The hydroxyl group of

10 phenol **12** is protected with a suitable protecting group, for example trityl, silyl, benzyl or MOM- etc to give **13** as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Treatment of **14** with **13** following the procedures described in US Patent No. 6197779 and WO 0027825 give **15**. Removal of the protecting group gives phenol **16**. Reaction of phenol **16** with phosphonate reagent **9** in the

15 presence of base in a protic solvent provides **4a**. Nitration (Scheme 4) of commercially available 2,6-dimethyl phenol provides **18**. Reduction of nitro group to amine, followed by protection of the resultant amine with protecting group, for example, such as trityl, Boc, Cbz etc as described in Greene and Wuts, Protecting Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons Inc. Treatment of **14a** with **19** following the procedures described in US

20 Patent No. 6197779 and WO 0027825 give **20**. Phenol **21** is obtained by treating **20** with

NH3 using the procedure described in US Patent No. 6197779 and WO 0027825, followed by removal of the protecting group. Reaction of phenol 21 with phosphonate reagent 9 provides 4b. As shown in Scheme 5, the commercially available 2,6-dimethyl-4-cyano-phenol 22 is reduced to benzyl amine, and the resultant amine is protected as described above. Phenol 23 is

5   converted to phosphonate 4c following the procedure described above for the transformation 19 to 4b, just replace 19 with 23. For example (Example 3), nitration of 2,6-dimethyl phenol with HNO₃ in H₂SO₄ gives phenol 18. The nitro group is reduced under catalytic hydrogenation condition, and subsequent protection of the resulting amine with Boc- gives phenol 19a. Treatment of phenol 18 with sodium hydride, followed by reacting the resulting

10 sodium phenoxide with 13 in dioxane provides 20a. Removal of the Boc- with TFA followed by treatment of the resulting product with NH₃ in isopropyl alcohol according to US Patent No. 6197779 and WO 0027825 replaces the Cl- with NH₂ group to give 21. The amine group in the phenyl ring is used as attachment site for introduction of phosphonate. Reductive amination of amine with aldehyde 9.3 provides 4b.1. Treatment of 21 with p-nitro-phenyl

15 carbonate, followed by aminoethyl phosphonate 9.4 affords urea linker 4b.2.

Scheme 3
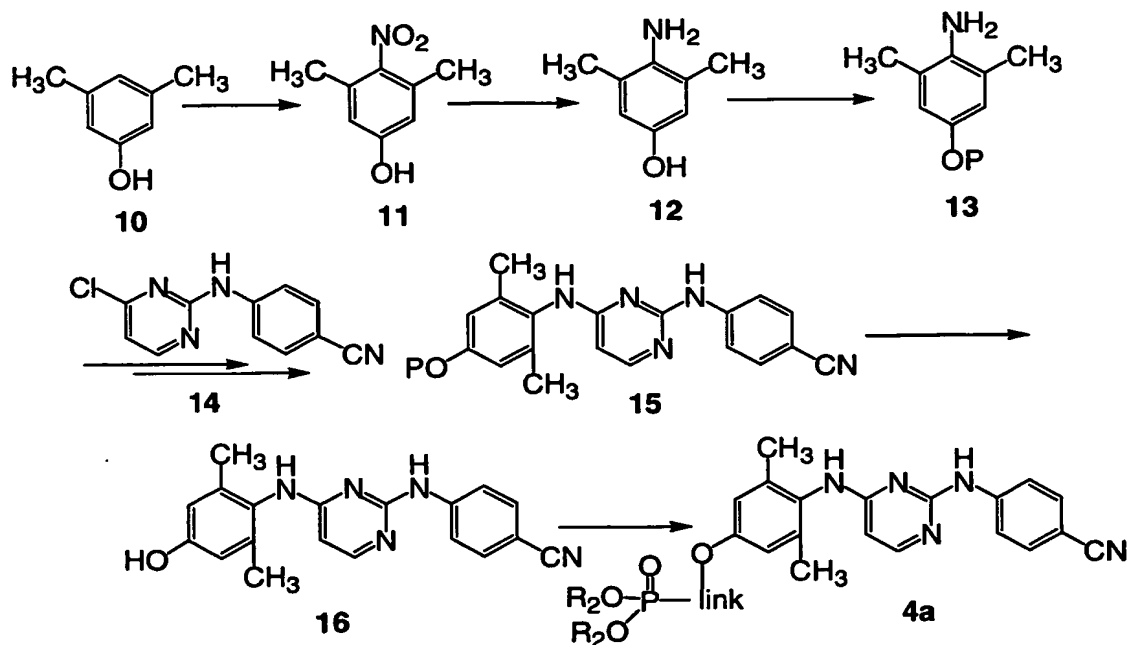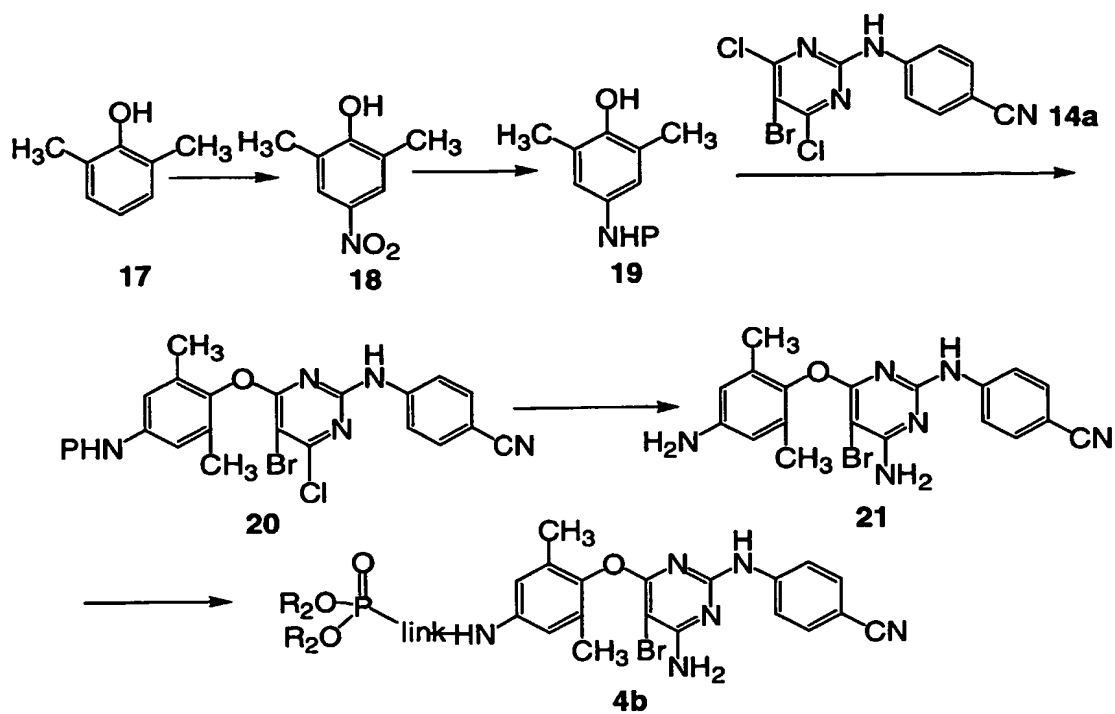
Scheme 4

Scheme 5

5
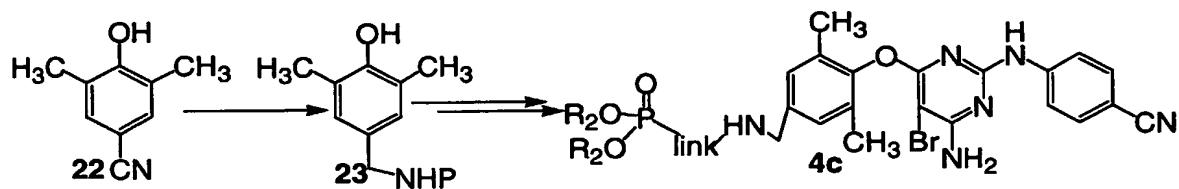
Example 3
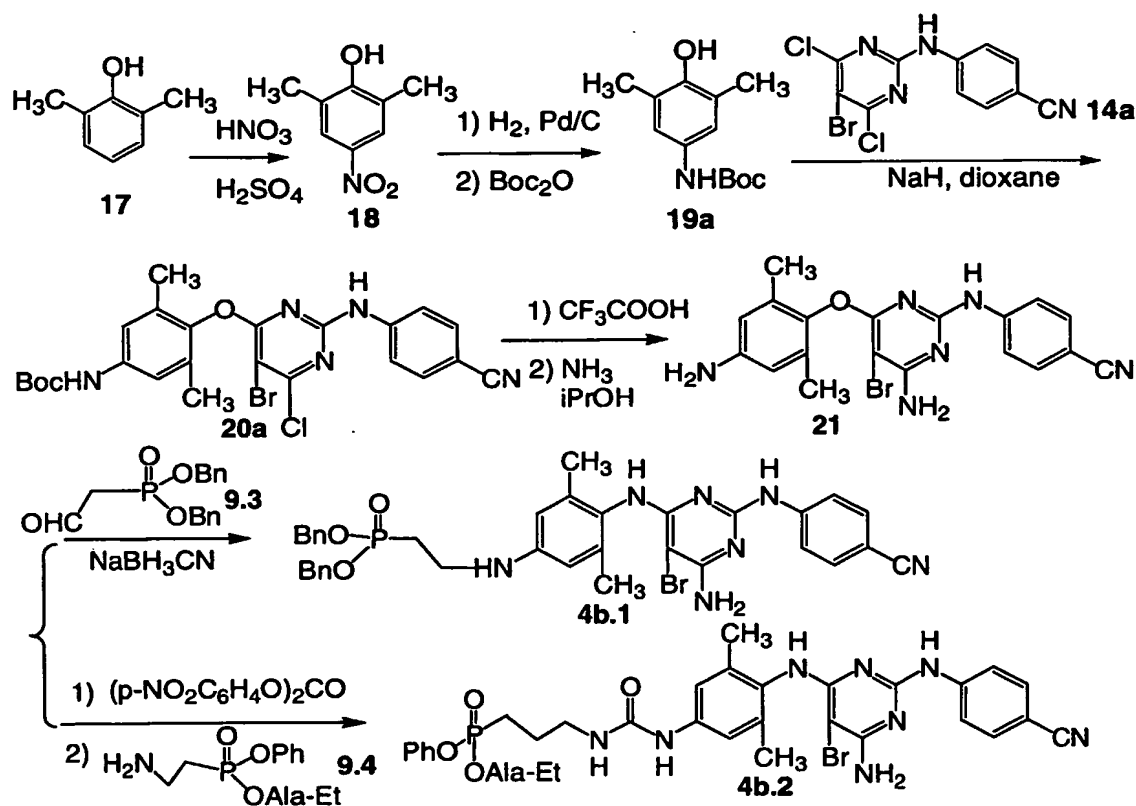
5   Scheme 6 shows the preparation of phosphonate type 6 in Figure 2. Substituted 4-amino-benzonitriles 24 or 27, which bearing a protected amino or hydroxyl group, or a precursor of amino group, are used in the replacement of 4-amino-benzonitrile for the preparation of TMC-125 and TMC-120 class of analogs as described in US Patent No. 6197779 and WO 0027825. TMC-120 and TMC-125 analogs 25 and 29 are thus obtained.

10   Removal of protecting group or conversion to amine group from a precursor, such as a nitro group, provide 26 or 30 respectively. Treatment of 26 and/or 30 with reagent 9 yield 6a and/or 6b respectively. For example (Example 4), the hydroxyl group of 4-amino-2-hyroxy-benzonitrile 27a is protected as its MOM-ether to give 28a. Following the procedure in US Patent No. 6197779 and WO 0027825, 28a is converted to TMC-120 analog 29a. Removal

15   of MOM-ether with TFA provides phenol 30a, which is treated with trifluoromethylsulfonyl phosphonic acid benzyl ester together with Cs_2CO_3 in acetonitrile affords phosphonate analog 6b.1.

Scheme 6
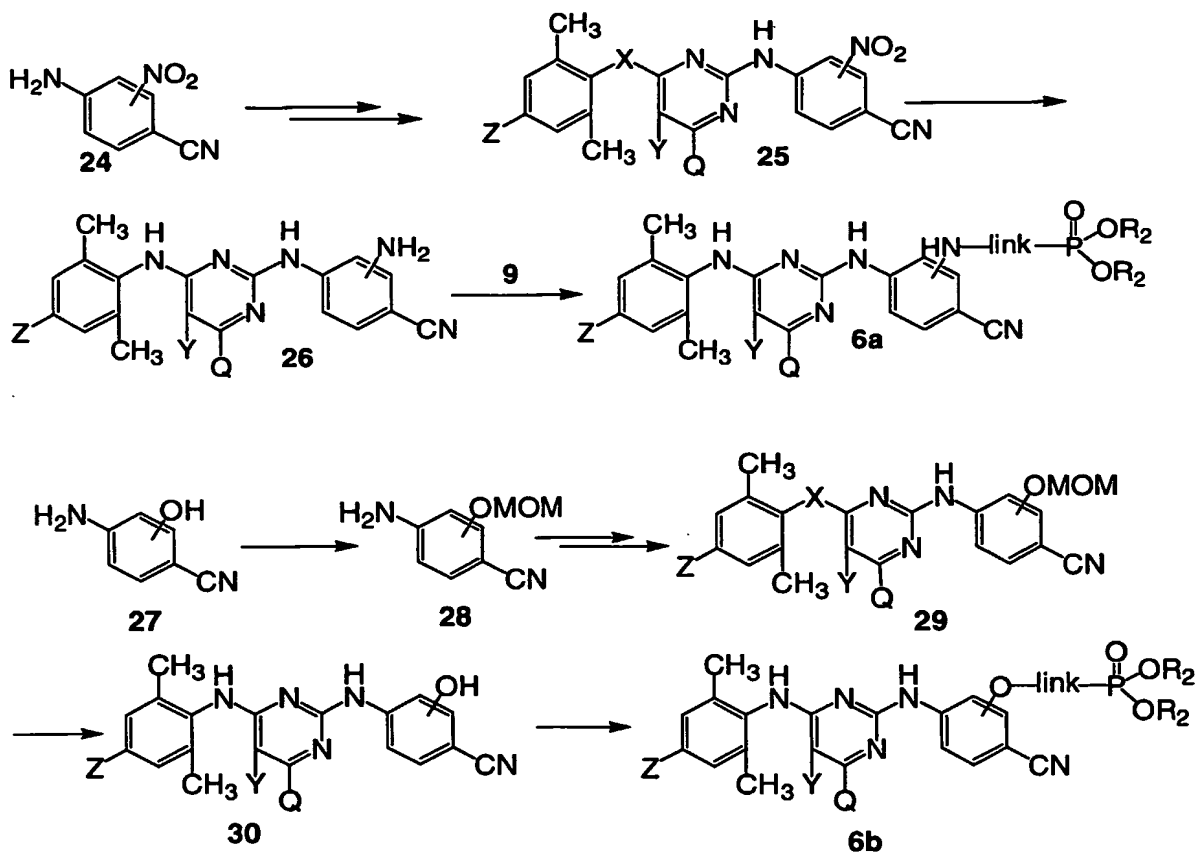
Example 4
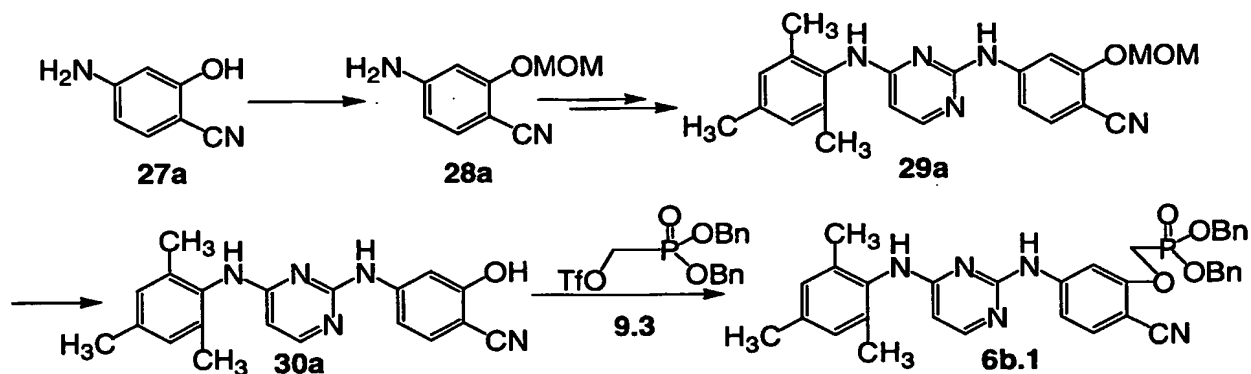
Preparation of phosphonate analog type 5 in Figure 2 is shown in Scheme 7. Substituted aniline, which bearing a protected amino or hydroxyl group, is converted to TMC-120 or TMC-125 analogs following the procedures described in US Patent No. 6197779 and WO 0027825. Removal of the protecting group gives analog 34. The amino or hydroxyl group in 33 serves as attachment site for introduction of phosphonate. Reaction of 33 with

reagent **9** provides **5a**. For example (Example 5), commercially available 2-amino-2,4,6-trimethyl-aniline is selectively protected as Boc- carbamate. Reaction of **32a** with **13** provides **33a**. Removal of Boc with TFA affords aniline **34a**. Reductive amination with reagent **9.2** yields phosphonate analog **5a.1**.

5

Scheme 7
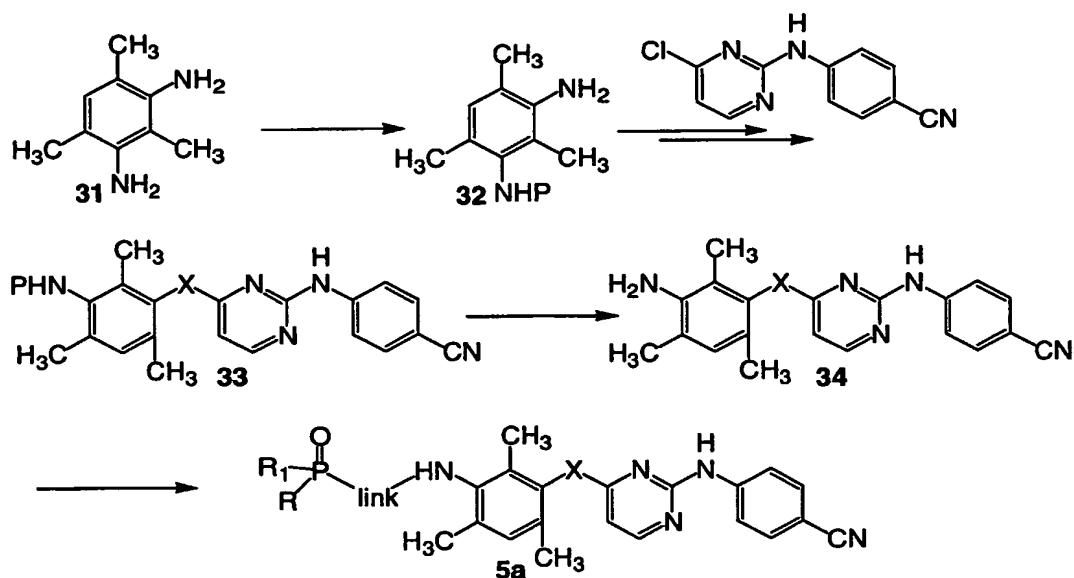
Example 6
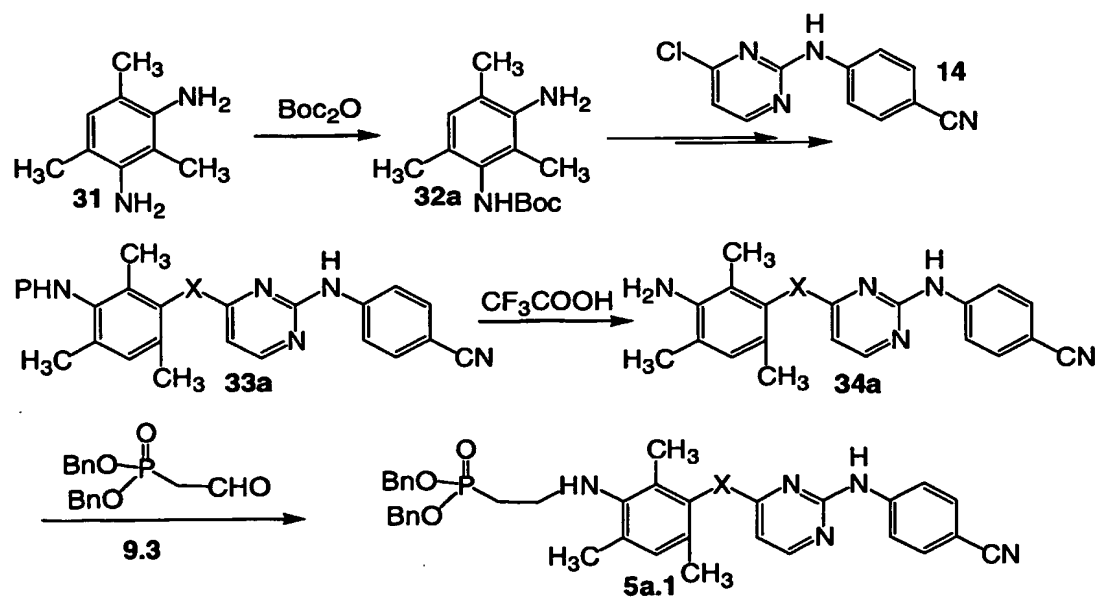
10

SJ3366-like phosphonate NNRTI compounds
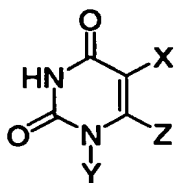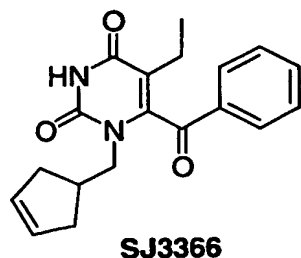
SJ3366

X = alkyl C_1-C_{12}branched or straight
Y = alkyl, alkoxy, with or without link-PO(R_1)(R_2)
Z= Y_2-link-PO(R_1)(R_2) or
    Y_2-Aryl (optionally substituted)
    or Y_2-alkyl
Y_2=CR_2, O, S, NR (R = H, alkyl C_1-C_{12}), C=O, COH

Type A [Y = link PO(R_1)(R_2)]

Type B [Z=link PO(R_1)(R_2)]

A1

B1
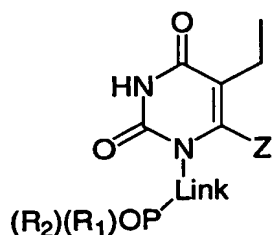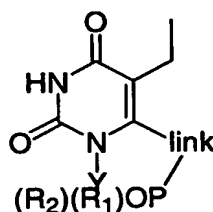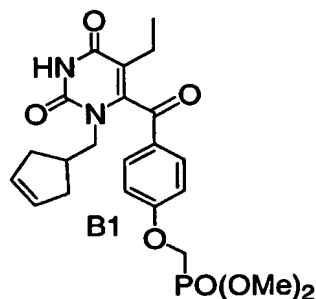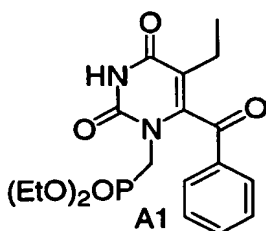
SJ3366 is described in US Patent No. 5922727. The present invention provides novel phosphonate analogs of SJ3366 which possess all the utilities of SJ3366 and optionally

5   provide cellular accumulation as set forth below.

The present invention also relates to the delivery of SJ3366-like phosphonate compounds which are optionally targeted for site-specific accumulation in cells, tissues or organs. More particularly, this invention relates to analogs of SJ3366 which comprise SJ3366 linked to a PO(R_1)(R_2) moiety.

10   SJ3366 may be covalently bonded directly or indirectly by a link to the PO(R_1)(R_2) moiety. An R group of the PO(R_1)(R_2) moiety can possibly be cleaved within the desired delivery site, thereby forming an ionic species which does not exit the cell easily. This may cause accumulation within the cell and can optionally protect the SJ3366 analog from

exposure to metabolic enzymes which would metabolize the analog if not protected within the cell. The cleavage may occur as a result of normal displacement by cellular nucleophiles or enzymatic action, but is preferably caused to occur selectively at a predetermined release site. The advantage of this method is that the SJ3366 analog may optionally be delivered site-

5   specifically, may optionally accumulate within the cell and may optionally be shielded from metabolic enzymes.

The following examples illustrate various aspects of the present invention and are not to be construed to limit the types of analogs that may employ this strategy of linking SJ3366 or an SJ3366 analog to a $PO(R_1)(R_2)$ moiety in any manner whatsoever.

10   Preparation of compounds of type A require a link which can react with SJ3366 or an intermediate or analog thereof, to result in a covalent bond between the link and the drug-like compound. The link is also attached to the phosphorous containing moiety as shown in an example of type A, namely A1.

Examples of type A can be made by 1-alkylation of the 3-phenacyl derivatives 35 and

15   36 (synthesis described in J. Med. Chem. 1995, 38, 1860-2865, and so numbered 35 and 36 therein) with alkyl halide containing links followed by deprotection of the 3-phenacyl group. An example synthesis is as follows, and is shown in Scheme 1. 6-Benzyl-5-isopropyl-3-(2-phenyl-allyl)-dihydro-pyrimidine-2,4-dione, as prepared in J. Med. Chem. 1995, 38, 15, 2860-2865, is treated analogously to the reference article authors' treatment in preparing their

20   compounds 37-40, but in the case of compound A1, commercially available chloromethyldiethylphosphonate is used as the alkylating agent. Alternatively the link is connected by starting with the same drug-like compound and using a triflated link. The triflated link is prepared, for example, by reaction of allyl bromide with dibenzylphosphite and potassium carbonate in acetonitrile at 65°C. Ozonolysis of the double bond followed by

25   treatment with sodium borohydride would provide the alcohol, which could then be reacted with triflic anhydride with 2,6 lutidine in dichloromethane to produce the triflate. The triflated material could then be attached by stirring it with, for example 6-Benzyl-5-isopropyl-3-(2-phenyl-allyl)-dihydro-pyrimidine-2,4-dione with 2,6 lutidine or other base in an appropriate solvent such as acetone. This procedure will provide examples A1 and A2.

30

Scheme 1

6-Benzyl-5-isopropyl-3-(2-oxo-2-phenyl-ethyl)
-5*H*-pyrimidine-2,4-dione   A1
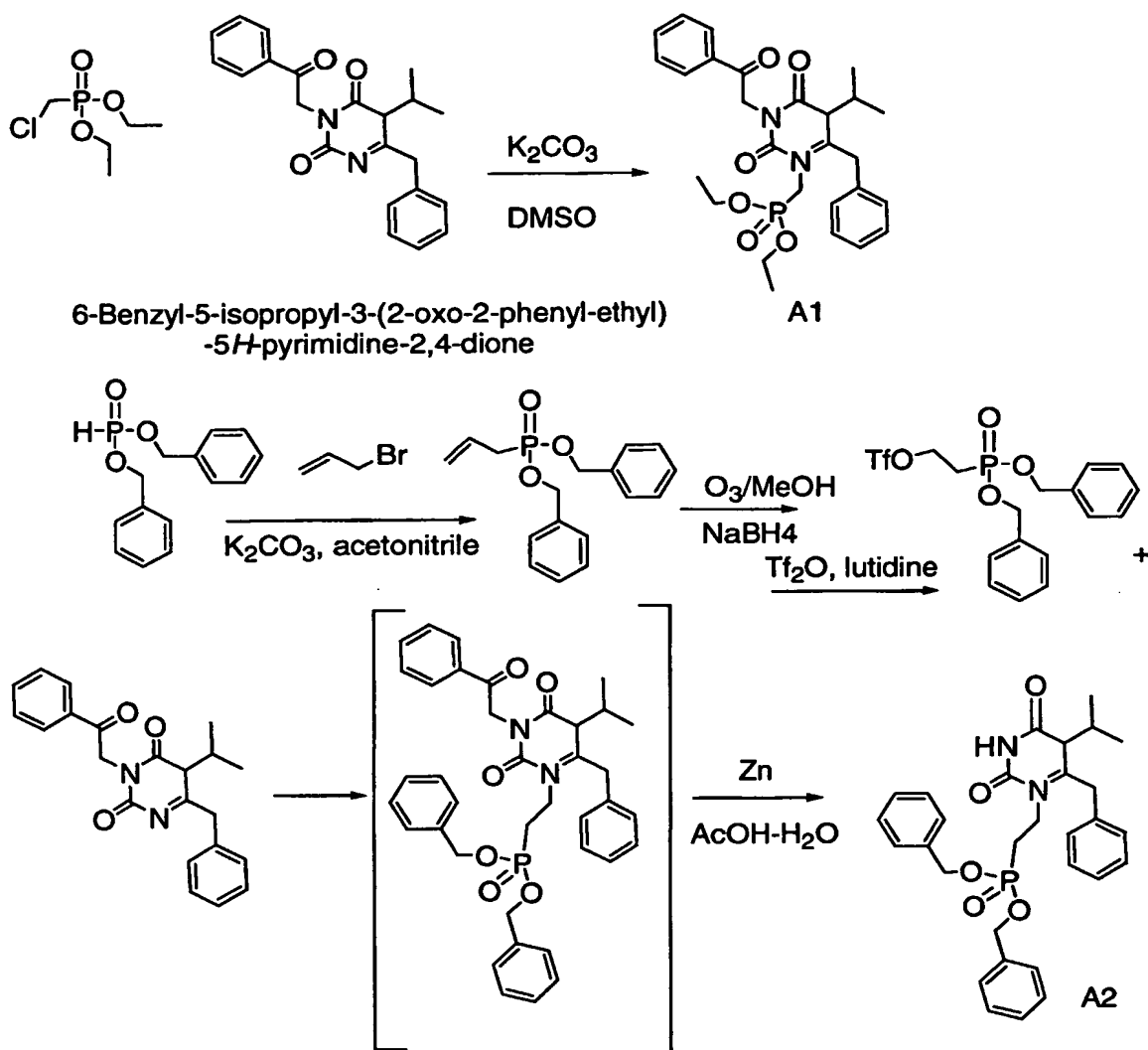
Scheme 1 can be extended to include analogs with various moieties at C6 in addition to

substituted benzyl rings. For example, the LDA treatment described in J. Med. Chem. 1995,

38, 15, 2860-2865 followed by disulfide addition provides intermediates which can then be

treated similarly to those in scheme 1 to install the link $PO(R_1)(R_2)$ at the 1 position

Scheme 2
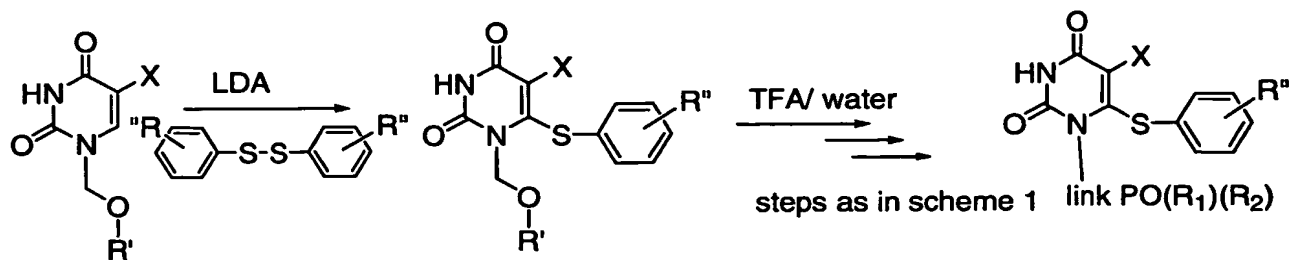
5   Scheme 3 also demonstrates a method to prepare analogs with oxygen or nitrogen at Y_2 attached to the 6 position. This method is explained fully in J. Med. Chem. 1991, 34,1, 349 - 357. Using this method allows for aryl and alkyl groups to be attached to the 6 position by either oxygen or nitrogen. A specific example is shown in the bottom row of the boxes in Scheme 7 below.

10

Scheme 3
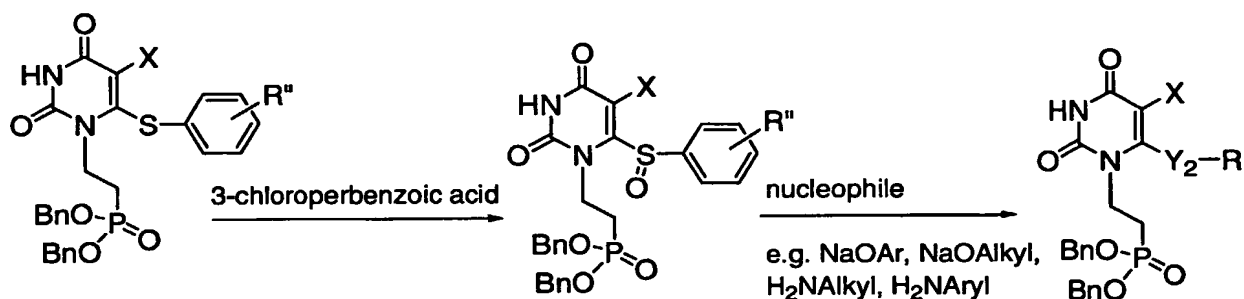
15   Alternatively the 5 position may be functionalized after the nucleophile is appended by the TFA/water deprotection and alkylation strategy shown in Scheme 2. Analogs with methylene, a secondary alcohol or a ketone at the 6 position are readily prepared following the LDA procedure in Scheme 2, but using substituted or unsubstituted PhCOCl in place of a disulfide, as is done in J. Med. Chem. 1991, 34, 1 page 351. The resultant ketone can be

20   converted to an oxime ether (Scheme 4), an ether (Scheme 5) or reduced to a methylene (Scheme 6). Scheme 6 can be extended with the deprotection and alkylation steps described in Scheme 2. The methylene, secondary alcohol and ether are all described in J. Med. Chem.

1991, 34, 1 page 349-357, and the oxime ether can be prepared as described below (Scheme 4).

Scheme 4

5
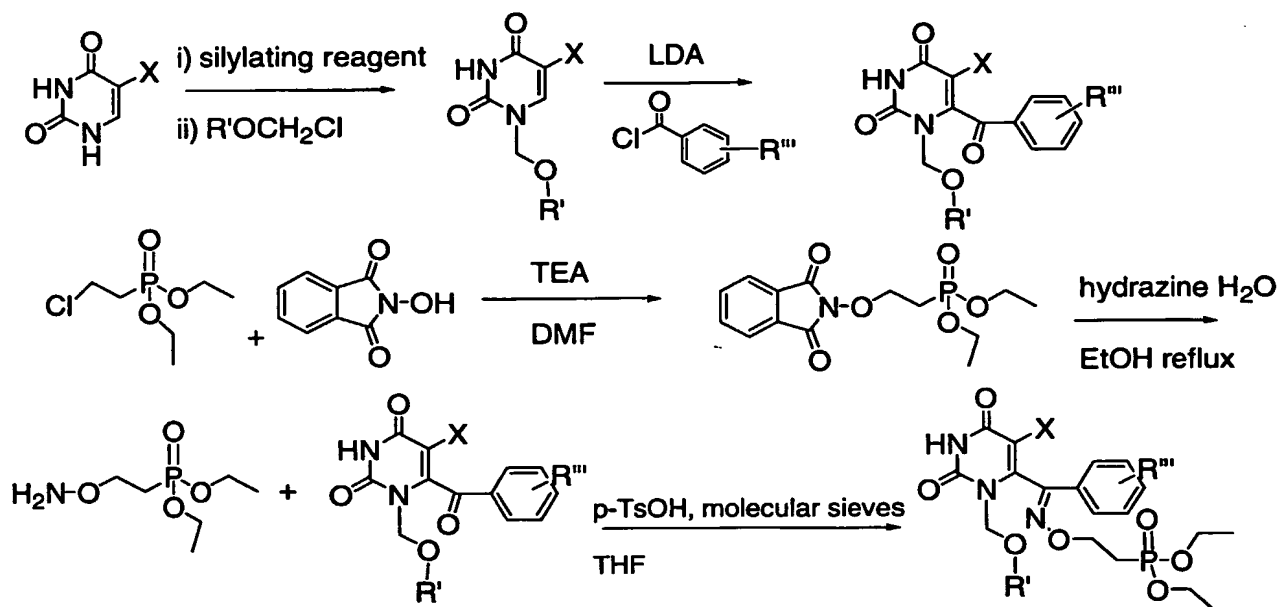
Alternatively the ketone containing compound could undergo deprotection at the 1 position and attachment of the link $PO(R_1)(R_2)$ as in Scheme 2 above.

10

Scheme 5

15
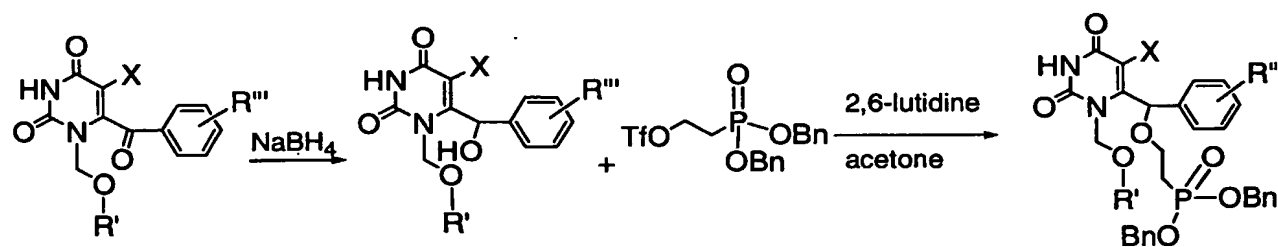
Scheme 6
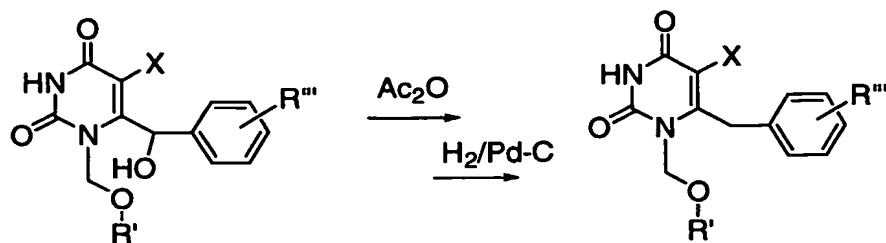
5   The above shown compounds could also have a reactive group at the aryl or alkyl

substituent on the 5 or the 6 position that would allow for attachment of the $PO(R_1)(R_2)$

group. These reactive groups are protected by a protecting group, or be present in the form

of a masked functionality, such as the manner in which a nitro group would mask an amine.

Scheme 7 shows some more representative examples of the many ways an attachment of a

10     $PO(R_1)(R_2)$ is made. The chemistry involved is explained above, except for the BBr3

demethylation, which is a common procedure (J.F.W.McOmie and D.E. West, Org. Synth.

Collect. Vol. V, 412, (1973) for demethylating methoxyaryl rings. The compounds in box A

are treated with hydrogen gas and stirred in a solvent such as ethanol or methanol with a

suspension of 10% palladium on carbon. The anilines or alcohols are then treated with a

15   triflated $PO(R_1)(R_2)$ containing group as described above.

Scheme 7

A   B   C
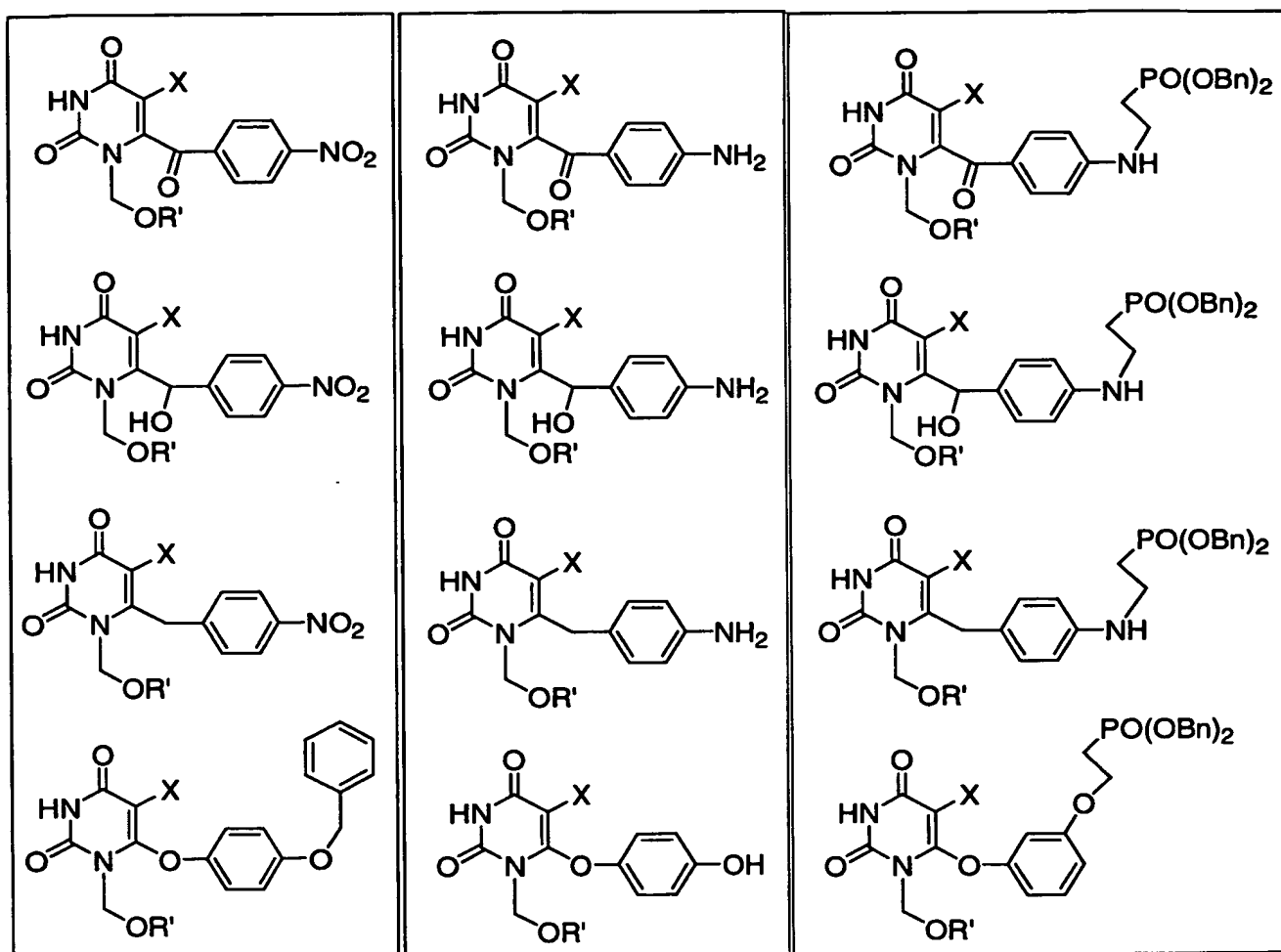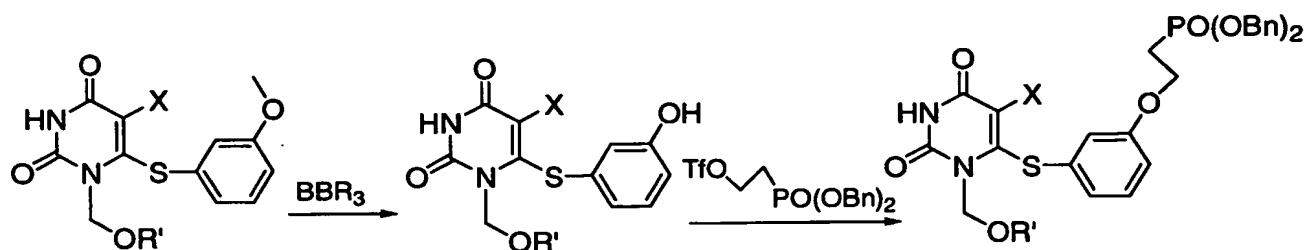
Delavirdine-like phosphonate NNRTI compounds

Diaromatic compounds refer to any diaromatic substituted compound, more specifically, bis(heteroaryl) piperazine (BHAP), more specifically 1{5-methanesulfonamidoindolyl-2-carbonyl}-4-{3-(1-methylethylamino)-2-pyridinyl}piperazine as

found in US Patent No. 5563142 claim 8 column 90 line 49-51, and pharmaceutically
acceptable salts thereof.

Delavirdine
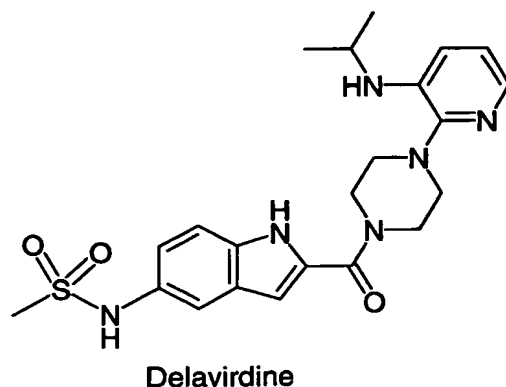
5   Preparation of compounds of type A, B, and C require a link which can react with a
drug-like compound which is either 1{5-methanesulfonamidoindolyl-2-carbonyl}-4-{3-(1-
methylethylamino)-2-pyridinyl}piperazine or an intermediate thereof, to result in a covalent
bond between the link and the drug-like compound. The link is also attached to the
phosphorous containing moiety shown in examples of type A, B and C, namely A1, B1 and
10   C1.

Scheme 1
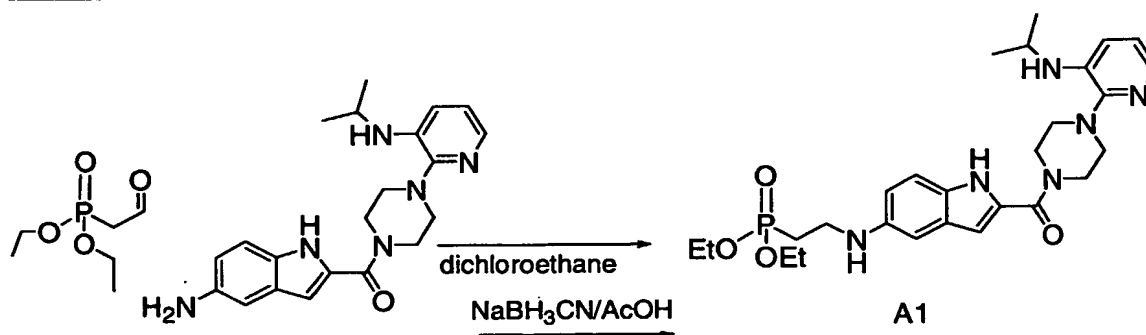
15   Examples of type A can be made by reacting the aminoindole NH_2 of the immediate
precursor to delavirdine (1-[5-amidoindolyl-2-carbonyl]-4-[3-(1-methylethylamino)-2-
pyridinyl]piperazine, such as example 101 in US Patent No. 5563142, synthesis described

therein, with the phosphorous containing moiety having an aldehyde as the reactive part of the link. The aldehyde and NH₂ group react through a reductive amination reaction, which can be performed by stirring both reagents in, for example dichloroethane, for approximately two hours and then adding acetic acid and sodium cyanoborohydride, or by other standard

5   methods known to most organic chemists. Commercially available aldehyde containing phosphonates such as that shown in the below scheme 1 can be used to prepare example A1.

This method may be extended to synthesize molecules with the link attached at other positions on the indole phenyl ring by following the procedures described in US Patent No. 5563142 but substituting starting materials as relevant to obtain the indole with the desired

10   substitution pattern.

Examples of type B can be prepared by reacting the indole NH of delavirdine with, for example, a link which contains an alkyl chloride in the presence of KOH in DMSO as described in J. Med. Chem. 34, 3, 1991, 1099-1110. The alkyl chloride link is for example commercially available chloromethyl diethoxyphosphonate, giving example B1.

15

Scheme 2

B1
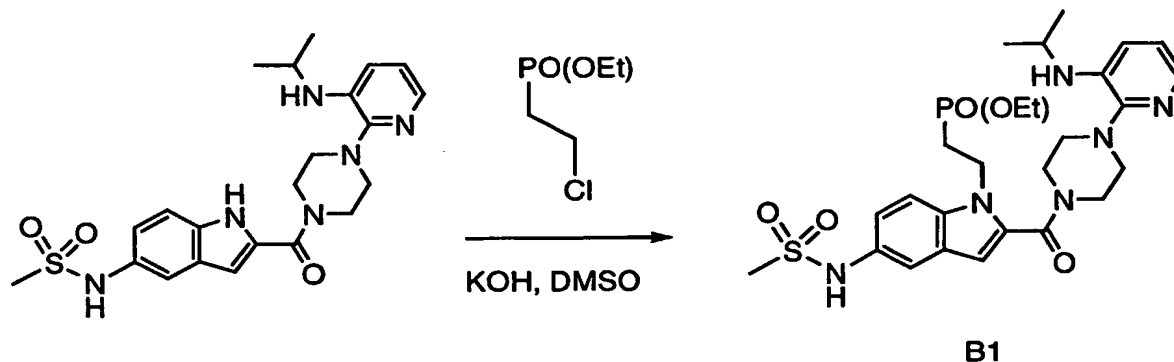
Examples of type C can be made by reacting the secondary amine of delavirdine with

20   the phosphorous containing moiety having an aldehyde as the reactive part of the link. The aldehyde and NH group react through a reductive amination reaction, which can be performed by stirring both reagents in, for example dichloroethane, for approximately two hours and then adding acetic acid and sodium cyanoborohydride, or by other standard methods known to most organic chemists. In this example the aldehyde containing phosphonate is commercially

25   available. This procedure will provide example C1.

Scheme 3

C1

B1

C1

Type C

Type B

Type A

5
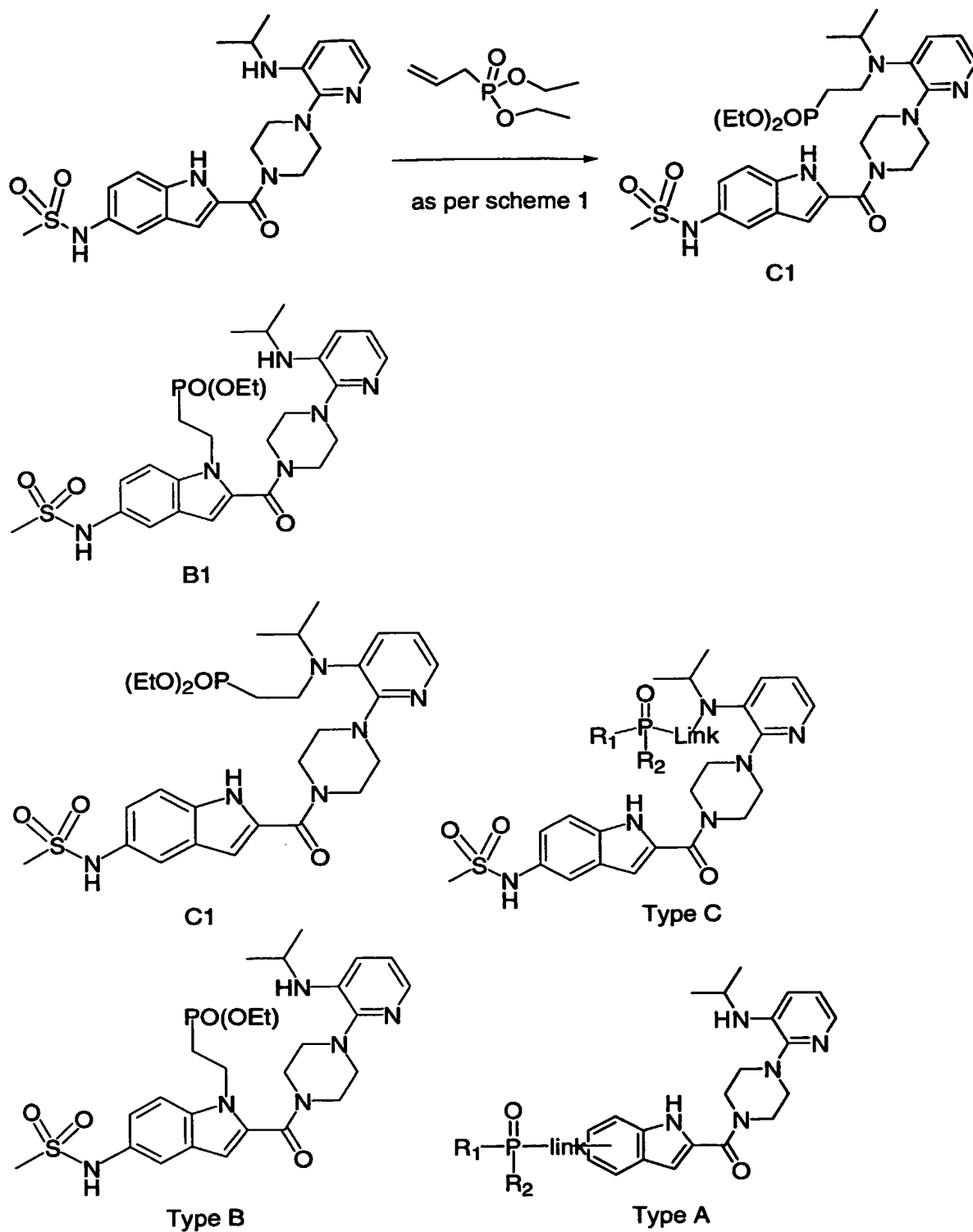
The present invention provides novel analogs of 1{5-methanesulfonamidoindolyl-2-carbonyl}-4-{3-(1-methylethylamino)-2-pyridinyl}piperazine. Such novel 1{5-methanesulfonamidoindolyl-2-carbonyl}-4-{3-(1-methylethylamino)-2-pyridinyl}piperazine

analogs possess all the utilities of 1{5-methanesulfonamidoindolyl-2-carbonyl}-4-{3-(1-methylethylamino)-2-pyridinyl}piperazine and optionally provide cellular accumulation as set forth below.

Emivirine-like phosphonate NNRTI compounds
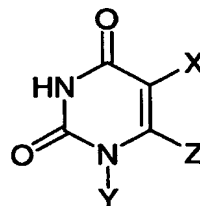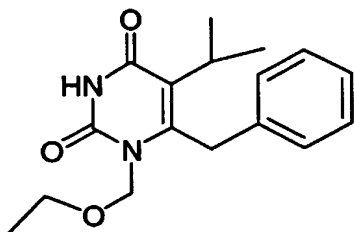
X = alkyl C_1-C_{12} branched or straight
Y = alkyl, alkoxy, with or without link-$PO(R_1)(R_2)$
Z = Y^2-link-$PO(R_1)(R_2)$ or
     Y^2-Aryl (optionally substituted)
     or Y^2-alkyl
Y^2=CR_2, O, S, NR (R = H, alkyl C_1-C_{12}), C=O, COH

Type A [Y = link $PO(R_1)(R_2)$]

Type B [Z=link $PO(R_1)(R_2)$]

A1

B1
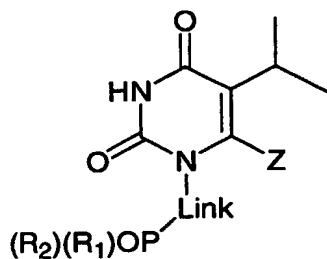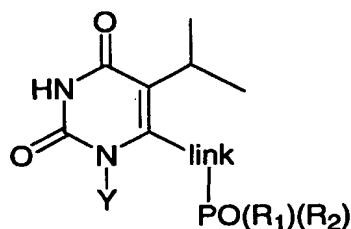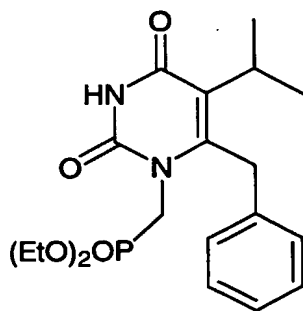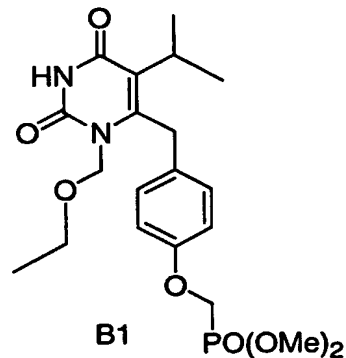
The present invention provides novel phosphonate analogs of Emivirine and pharmaceutically acceptable salts thereof. Emivirine is described in US Patent No. 5461060. Such novel Emivirine analogs possess all the utilities of Emivirine and optionally provide cellular accumulation as set forth below.

The present invention also relates to the delivery of Emivirine-like phosphonate compounds which are optionally targeted for site-specific accumulation in cells, tissues or

organs. More particularly, this invention relates to analogs of Emivirine which comprise Emivirine linked to a $PO(R_1)(R_2)$ moiety.

Emivirine is covalently bonded directly or indirectly by a link to the $PO(R_1)(R_2)$ moiety. An R group of the $PO(R_1)(R_2)$ moiety can possibly be cleaved within the desired

5   delivery site, thereby forming an ionic species which does not exit the cell easily. This may cause accumulation within the cell and can optionally protect the Emivirine analog from exposure to metabolic enzymes which would metabolize the analog if not protected within the cell. The cleavage may occur as a result of normal displacement by cellular nucleophiles or enzymatic action, but is preferably caused to occur selectively at a predetermined release site.

10   The advantage of this method is that the Emivirine analog may optionally be delivered site-specifically, may optionally accumulate within the cell and may optionally be shielded from metabolic enzymes.

Link: an atom or molecule which covalently binds together two components. In the present invention, a link is intended to include atoms and molecules which can be used to

15   covalently bind Emivirine or an analog thereof at one end of the link to the $PO(R_1)(R_2)$ at the other end of the link. The link must not prevent the binding of the analog with its appropriate receptor. Examples of suitable links include, but are not limited to, polymethylene [--$(CH_2)_n$, where n is 1-10], ester, amine, carbonate, carbamate, ether, olefin, aromatic ring, acetal , heteroatom containing ring, or any combination of two or more of these units. The

20 $PO(R_1)(R_2)$ may also be directly attached. A skilled artisan will readily recognize other links which can be used in accordance with the present invention.

The preceding Schemes 1-7 for SJ3366-like phosphonate NNRTI compounds illustrate various aspects of the present invention and are not to be construed to limit the types of analogs that may employ this strategy of linking Emivirine or an Emivirine analog to a

25   $PO(R_1)(R_2)$ moiety in any manner whatsoever.

Loviride-like phosphonate NNRTI compounds

The present invention relates to Loviride-like phosphonate NNRTI compounds and their delivery to cells, tissue or organs which are optionally targeted for site-specific

30   accumulation. More particularly, this invention relates to phosphonate analogs of Loviride, and their pharmaceutically acceptable salts and formulations, which comprise Loviride linked to a phosphonate, i.e. $PO(R_1)(R_2)$ moiety.

The groups R_1-R_{10} are as described in US Patent No. 5556886, and also can be link

$PO(R_1)(R_2)$. The present invention provides novel phosphonate analogs of Loviride. Such

novel Loviride analogs possess all the utilities of NNRTI properties as Loviride and optionally

provide cellular accumulation as set forth below.

5
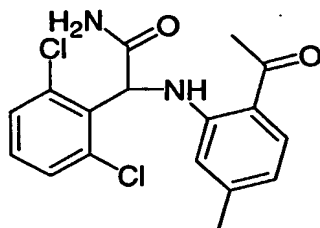
Loviride
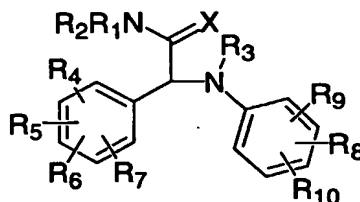
Loviride may be covalently bonded directly or indirectly by a link to the $PO(R_1)(R_2)$

moiety. An R group of the $PO(R_1)(R_2)$ moiety can possibly be cleaved within the desired

10   delivery site, thereby forming an ionic species which does not exit the cell easily. This may

cause accumulation within the cell and can optionally protect the Loviride analog from

exposure to metabolic enzymes which would metabolize the analog if not charged or protected

within the cell. The cleavage may occur as a result of normal displacement by cellular

nucleophiles or enzymatic action, but is preferably caused to occur selectively at a

15   predetermined release site. The advantage of this method is that the Loviride analog may

optionally be delivered site-specifically, may optionally accumulate within the cell and may

optionally be shielded from metabolic enzymes.

The following examples illustrate various aspects of the present invention and are not

to be construed to limit the types of analogs that may employ this strategy of linking Loviride

20   or an Loviride analog to a $PO(R_1)(R_2)$ moiety in any manner whatsoever.

UC781-like phosphonate NNRTI compounds
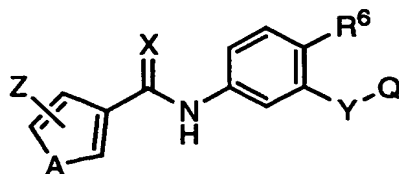
5   The present invention includes UC781-like phosphonate compounds and

pharmaceutically acceptable salts thereof. UC781 is described in US Patent No. 6143780.

A, X, Y, Q and R^6 in the formula above are as defined in US Patent No. 6143780. Z

represents any substitution of the heteroatom ring. Also the heteroatom ring may be six

membered. The present invention provides novel phosphonate analogs of UC781. Such novel

10   UC781 analogs possess all the utilities of Emivirine and optionally provide cellular

accumulation as set forth below. The present invention also relates to the delivery of UC781-

like phosphonate compounds which are optionally targeted for site-specific accumulation in

cells, tissues or organs. More particularly, this invention relates to analogs of UC781 which

comprise UC781 linked to a $PO(R_1)(R_2)$ moiety.

15   UC781 is covalently bonded directly or indirectly by a link to the $PO(R_1)(R_2)$ moiety.

An R group of the $PO(R_1)(R_2)$ moiety can possibly be cleaved within the desired delivery site,

thereby forming an ionic species which does not exit the cell easily. This may cause

accumulation within the cell and can optionally protect the UC781e analog from exposure to

metabolic enzymes which would metabolize the analog if not protected within the cell. The

20   cleavage may occur as a result of normal displacement by cellular nucleophiles or enzymatic

action, but is preferably caused to occur selectively at a predetermined release site. The

advantage of this method is that the UC781 analog may optionally be delivered site-

specifically, may optionally accumulate within the cell and may optionally be shielded from

metabolic enzymes.

25   Link is any moiety which covalently binds together UC781 or an analog of UC781 and

a phosphonate group. In the present invention, a link is intended to include atoms and

molecules which can be used to covalently bind UC781 or an analog thereof at one end of the

link to the $PO(R_1)(R_2)$ at the other end of the link. The link should not prevent the binding of

the analog with its appropriate receptor. Examples of suitable links include, but are not

30   limited to, polymethylene [--$(CH_2)_n$, where n is 1-10], ester, amine, carbonate, carbamate,

ether, olefin, aromatic ring, acetal, heteroatom containing ring or any combination of two or more of these units. Direct attachment of the $PO(R_1)(R_2)$ is also possible. A skilled artisan will readily recognize other links which can be used in accordance with the present invention.

5 The following examples illustrate various aspects of the present invention and are not to be construed to limit the types of analogs that may employ this strategy of linking UC781 or an UC781 analog to a $PO(R_1)(R_2)$ moiety in any manner whatsoever.

Preparation of compounds of type A may proceed via a link which can react with UC781 or an analog or intermediate thereof, to result in a covalent bond between the link and the drug-like compound. The link is also attached to the phosphorous containing moiety as

10 shown in an example of type A, namely A1.

Preparation of N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-3-furancarbothioamide, compound 12 in scheme 1 and intermediates 2, 4-11, as per US Patent No. 6143780.

15 Step 1: Preparation of 2-chloro-5-nitrobenzoyl alcohol 30 g of 2-chloro-5-nitrobenzaldehyde was dissolved in 500 mL of methanol and cooled to 0°C. A solution of 10 g of sodium borohydride in 100 mL of water was then added dropwise over 90 minutes while maintaining the temperature below 10°C. The resultant reaction mixture was then stirred for one hour, then acidified with 2N HCl and left stirring overnight. The solids were then, washed with

20 water and dried, to produce 27 g of 2-chloro-5-nitrobenzyl alcohol as a white solid.

Step 2: Preparation of 2-chloro-5-nitrobenzoyl acetate 27 g of the 2-chloro-5-nitrobenzyl alcohol prepared above in Step 1, was dissolved in 122 mL of toluene. 22 mL of triethylamine was then added. The resultant reaction mixture was cooled to 20°C. and then a solution of

25 10.2 mL of acetyl chloride in 10 mL of toluene, was added dropwise, keeping the temperature below 20°C. The reaction mixture was then stirred overnight. 2.1 mL of triethylamine and 1.1 mL of acetyl chloride/toluene solution were then added and the reaction mixture was stirred for one hour. 100 mL of water was then added, followed by 50 mL of ether. The resulting organic phase was separated, washed with 2N HCl, aqueous sodium bicarbonate

30 solution and water. The washed organic phase was then dried over magnesium sulfate and the solvent was evaporated, to produce 29.6 g of 2-chloro-5-nitrobenzoyl acetate as a white solid.

Step 3: Preparation of 5-amino-2-chlorobenzoyl acetate 24 g of iron powder was added to a solution of 1.6 mL of concentrated HCl, 16.8 mL of water, and 70 mL of ethanol. 29.6 g of the 2-chloro-5-nitrobenzoyl acetate prepared above in Step 2 dissolved in 45 mL of ethanol, was then added to the mixture in three equal portions. The resultant reaction mixture was

5   refluxed for 5 hours. An additional 2.4 g of iron and 0.1 mL of concentrated HCl was then added to the reaction mixture. The reaction mixture was then refluxed for an additional one hour, filtered through Celite and evaporated. 100 mL of water was then added to the evaporated material and the resultant mixture was extracted with 100 mL of ether. The ether solution was washed with water, dried over magnesium sulfate, and evaporated, to produce

10   22.9 g of 5-amino-2-chlorobenzoyl acetate as an oil.

Step 4: Preparation of N-(3-acetoxymethyl-4-chlorophenyl)-2-methyl-3-furancarboxanilide. A solution of 22.8 g of the 5-amino-2-chlorobenzoyl acetate from Step 3 above and 17.2 mL of triethylamine in 118 mL ether was prepared and then added dropwise to a second solution

15   of 16.6 g 2-methyl-3-thiophenecarboxylic acid chloride in 118 mL ether at 0°C. to 10°C.and the resultant mixture was stirred at room temperature overnight. 100 mL of water and 100 mL of ethyl acetate were then added to the mixture, the organic phase separated, washed with 2N hydrochloric acid and water, dried over magnesium sulfate, and the solvents removed *in vacuo*, to produce 29.87 g of N-(3-acetoxymethyl-4-chlorophenyl)-2-methyl-3-

20   furancarboxamide as a beige solid.

Step 5: Preparation of N-(4-chloro-3-hydroxymethylphenyl)-2-methyl-3-furancarboxamide. A solution of 29 g of the N-(3-acetoxymethyl-4-chlorophenyl)-2-methyl-3-furancarboxamide prepared in Step 4 above and 14.5 g potassium hydroxide in 110 mL water, was prepared. The

25   solution was then heated at 70°C. for 16 hours and then acidified with 2N hydrochloric. The resulting solid was collected, washed with water, and dried, producing 23.65 g of N-(4-chloro-3-hydroxymethylphenyl)-2-methyl-3-furancarboxamide as a white solid.

Step 6: Preparation of N-(3-bromomethyl-4-chlorophenyl)-2-methyl-3-furancarboxamide. 12

30   g of the N-(4-chloro-3-hydroxymethylphenyl)-2-methyl-3-furancarboxamide prepared in Step 5 above, was dissolved in 180 mL ethyl acetate. 1.8 mL of phosphorus tribromide was then added. The resultant mixture was stirred for 90 minutes at room temperature. 100 mL of water was then added to the mixture. The resultant organic phase was separated, washed with

water, aqueous sodium bicarbonate solution and water, and then dried over magnesium sulfate. The solvent was evaporated off to produce 12.97 g of N-(3-bromomethyl-4-chlorophenyl)-2-methyl-3-furancarboxamide as a solid.

5 Step 7: Preparation of N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-3-furancarboxamide. 2 g of the N-(3-bromomethyl-4-chlorophenyl)-2-methyl-3-furancarboxamide produced in Step 6, was dissolved in 20 mL of 2-butanone to produce a solution. 0.84 g of potassium carbonate, 0.79 g of 2-chlorophenol and 0.2 g of tetrabutylammonium bromide were then added to the solution. The resultant reaction mixture

10 was stirred at room temperature overnight, the solvents removed *in vacuo*, and the residue extracted with ethyl acetate, to produce a second solution. This second solution was washed with 2N aqueous sodium hydroxide and water, and then dried over magnesium sulfate. The solvent was removed to produce 2.7 g of a solid, which was purified by dissolving in ethyl acetate:hexane (20:80) and running the resultant solution through a plug of silica geL

15 Removal of solvent produced 2.0 g of N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-3-furancarboxamid e as a white solid.

Step 8: Preparation of N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-3-furancarbothioamide. 1.5 g of the N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-

20 3-furancarboxamide prepared in Step 7 above, 0.8 g of Lawesson's reagent (0.8 g) and 1.6 g of sodium bicarbonate were added to 35 mL of toluene, and the resultant reaction mixture was refluxed for five hours. The reaction mixture was then passed through a plug of neutral aluminum oxide, eluted with 1:1 ether/hexane and purified by column chromatography on silica gel, to produce 0.77 g of N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-3-

25 furancarbothioamide.

Scheme 1

extend to all available 5 and 6 membered, hetero and non hetero aromatic carboxylic acids

any nitrobenzaldehyde   any nitrobenzylalcohol

Lawesson's reagent or

or P_2S_5
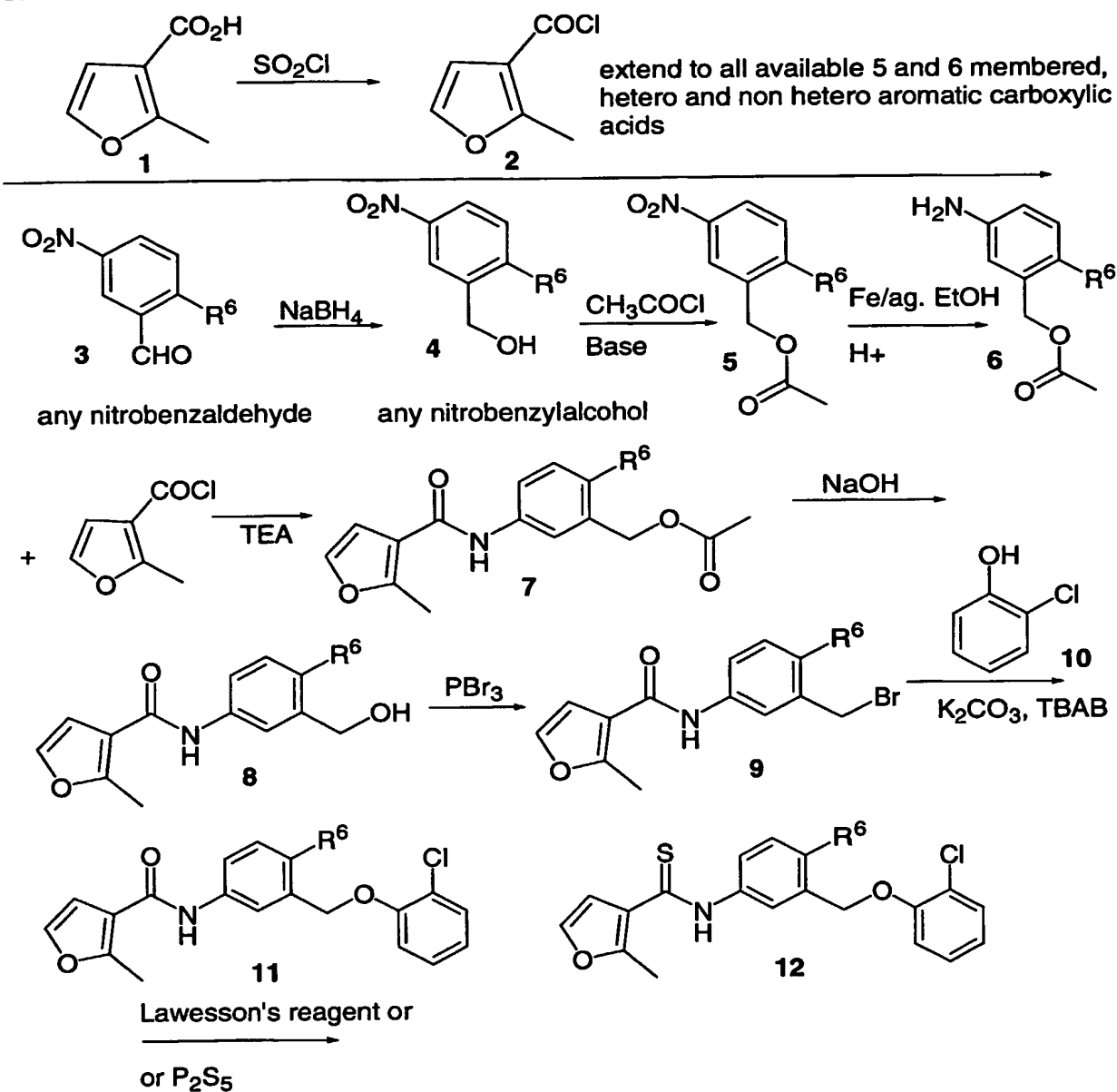
The above protocol can easily be modified to attach the link- $PO(R_1)(R_2)$.

To prepare compounds of type A in Figure 1, the following route is performed. Compound 8

5   above, when R^6 is chloro, is transformed into a triflate by reacting it with triflic anhydride and

2,6 lutidine in dichloromethane at -40°C. The addition of hydroxyethyldimethoxyphosphonate

will effect the attachment of the link $PO(R_1)(R_2)$ group. Treatment with Lawesson's reagent as

above will provide compound A2.

Figure 1

Type A   Example A1   Example A2
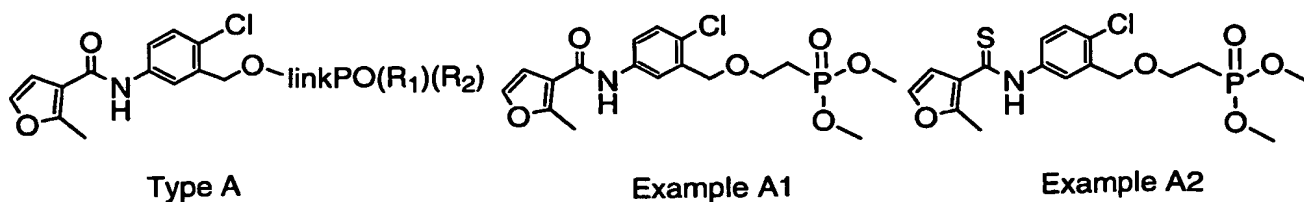
5   By replacing 2-chloro 5-nitrobenzaldehyde with other nitrobenzaldehyes and following a similar procedure as that used to make compound A2, the relative positions of attachment of the ether and the amide is changed. Furthermore, the chloro substituent shown as R^6 above is switched to other positions, and other substituents are used in combination with or without the chloro atom or other substituents anywhere on the ring (shown as Q below). This would

10   allow for compounds of type B2 of Figure 2 to be prepared. As with all analogs that are amenable to such treatment, Lawesson's reagent would then be used to convert to the corresponding sulfamide.

Figure 2

15
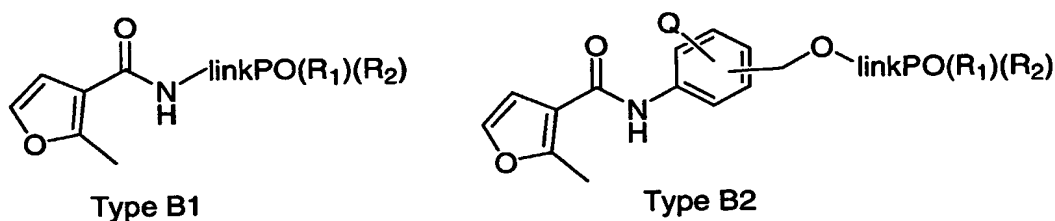
Type B1   Type B2

Type B1 compounds would include Type B2 and are prepared using the above steps with the center aryl ring being considered part of the link. Prior to treatment with Lawesson's reagent

20   the amide proton is abstracted by treatment with base to allow for attachment of the $PO(R_1)(R_2)$ moiety. Lawesson's reagent would then be used to convert to the corresponding sulfamide. This would allow for compounds of the general form Type C shown in Figure 3.

Figure 3

Type C
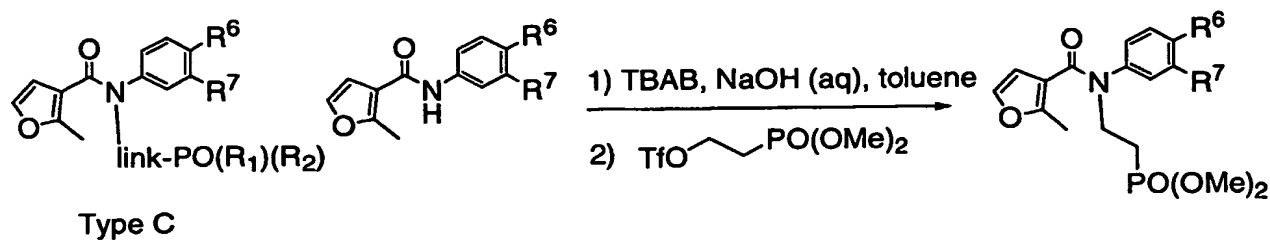
5

     The furan ring of UC781 is switched to 5 or 6-membered heterocycles easily by substituting different heterocyclic acid chlorides for 2-methyl-3-thiophenecarboxylic acid chloride in step 4 in the above written synthesis of N-3-((2-chlorophenoxy)methyl)-4-chlorophenyl-2-methyl-3-furancarbothioamide. This will afford Type D compounds as

10   exemplified below. The link $PO(R_1)(R_2)$ moiety is attached directly to the heterocycle by starting with for example the diester of the desired heterocycle. Mono acid formation of the heterocycle by hydrolysis of one ester would allow for attachment of the $PO(R_1)(R_2)$ group. This would be followed by hydrolysis of the remaining ester by base, acid chloride formation as above and amide formation by reaction with the desired amine. D1, a specific

15   exemplification of Type D compounds having in this case R_1 and $R_2 = OMe$ and link = CH_2CH_2 is prepared as shown below in Figure 4.

Figure 4

Type D   **5-membered heterocycle**   **6-membered heterocycle**
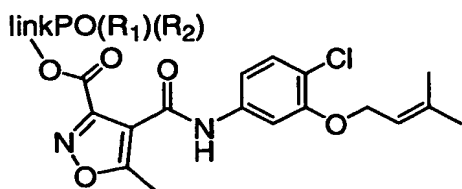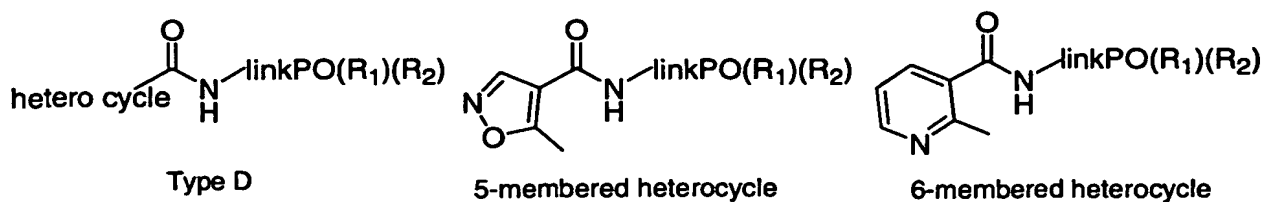
5-membered heterocycle
with linkPO(R₁)(R₂) attached at
heterocycle
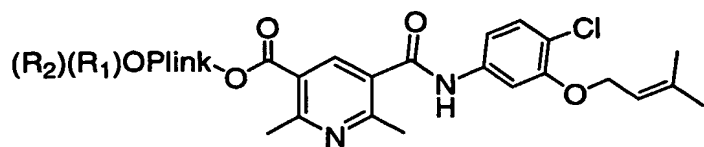
6-membered heterocycle
with linkPO(R₁)(R₂) attached at
heterocycle
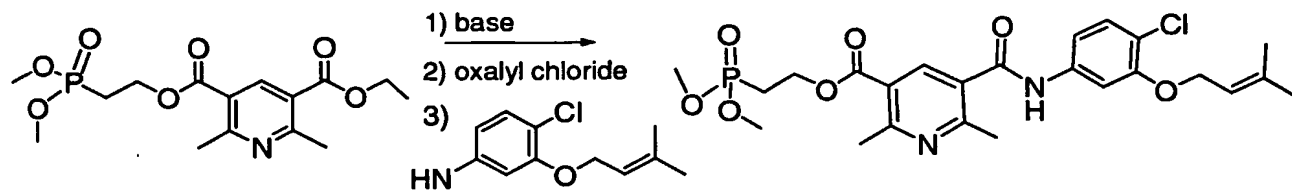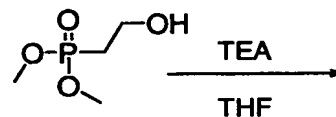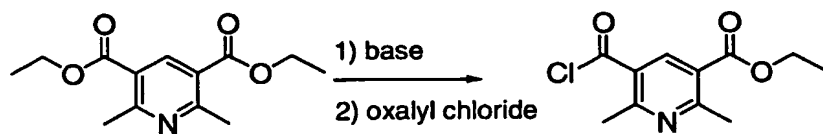
All amides shown can be converted to sulfamides by treatment with Lawesson's reagent.

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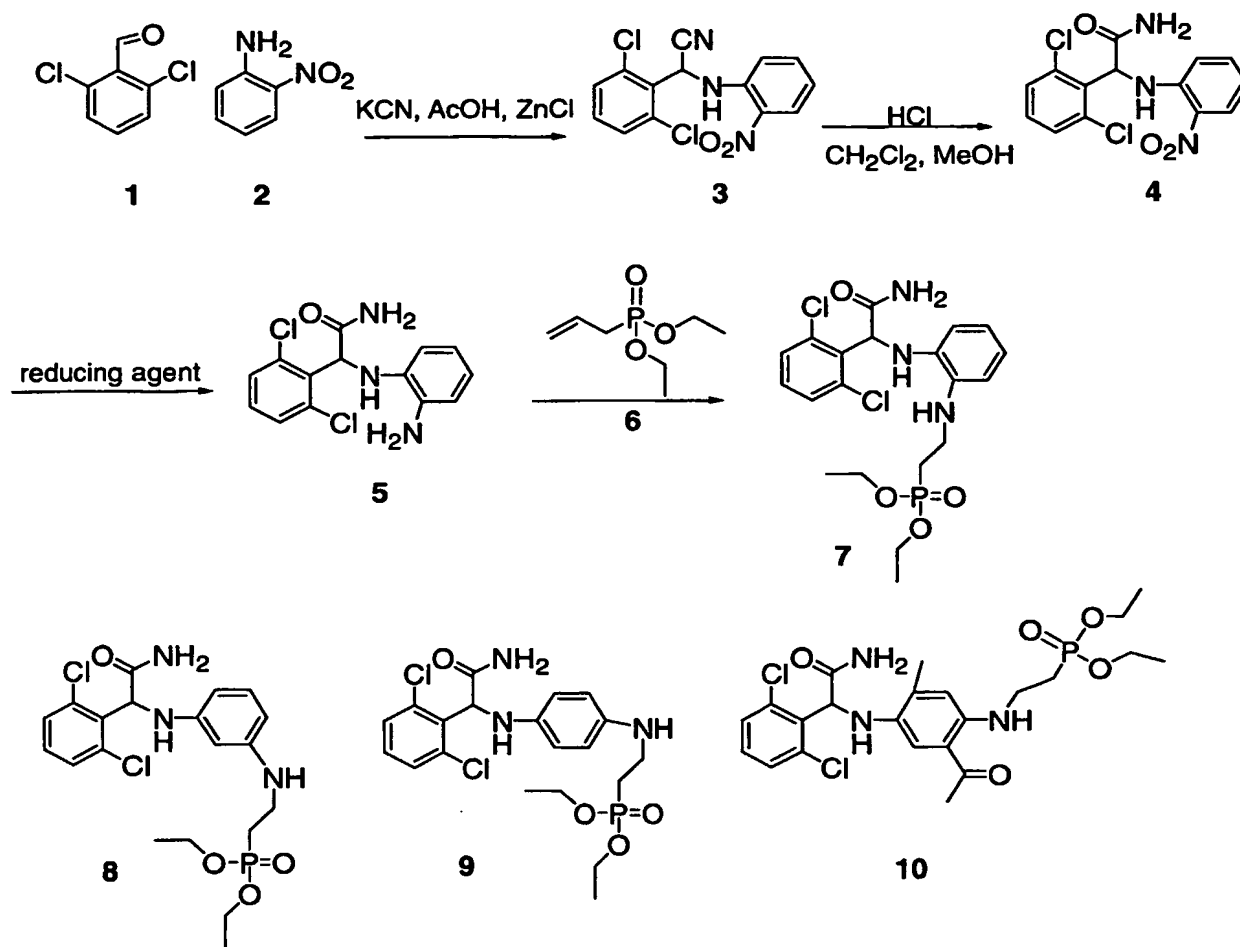
Scheme 1

5   The details of the first two steps of Scheme 1 shown above are thoroughly covered in
US Patent No. 5556886. The synthesis can be extended as shown to allow for the attachment
of the link $PO(R_1)(R_2)$ at various sites on either aryl ring.

To attach on the ortho, meta or para positions of the ring that starts out as the
substituted aniline, a moiety must be present that will allow for such an attachment of the

10    $PO(R_1)(R_2)$ moiety. In this case a nitro group is used as an amine precursor. The reduction
of the nitro can be effected by tin chloride and acetic acid in an appropriate solvent, or through
some other catalytic hydrogenation method. From there, compounds such as compound 5
with a free anilino NH_2 can be reacted with, for example, a commercially available
phosphonate such as compound 6 above in a reductive amination reaction. This reductive

15   amination is performed using dichloroethane as solvent, and after stirring under dry conditions,
sodium cyanoborohydride and acetic acid is added to complete the reaction giving compound

7. Using commercially available meta and para nitroanilines leads to compounds 8, 9 and 10. Other substitution patterns are also possible. Also, other means of attachment are also possible to attach the drug-like compound to the $PO(R_1)(R_2)$ piece. By varying the position of the nitro group, the $PO(R_1)(R_2)$ is attached at any position on the anilino ring. Figure 1 below contains examples of nitroanilines that allow for the attachment at various positions.

Alternatively, the nitroanilines is attached to the $PO(R_1)(R_2)$ moiety prior to coupling with the aldehyde. The nitro is then reduced to form the aniline needed for coupling with the aldehyde. Hydrolysis of the cyano group to the amide is conducted as above, as illustrated in Scheme 2.
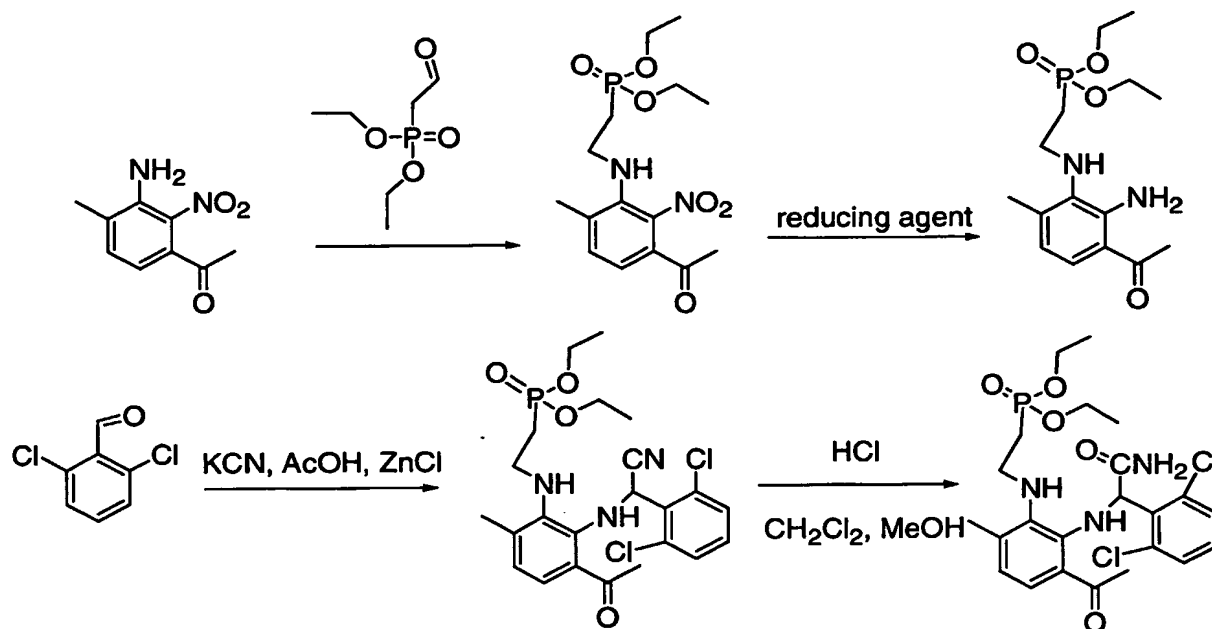
The ketone of Loviride or Loviride analogs also serves as a point of attachment for the $PO(R_1)(R_2)$ group. The synthesis of such an attachment is shown in Scheme 3.

Scheme 3
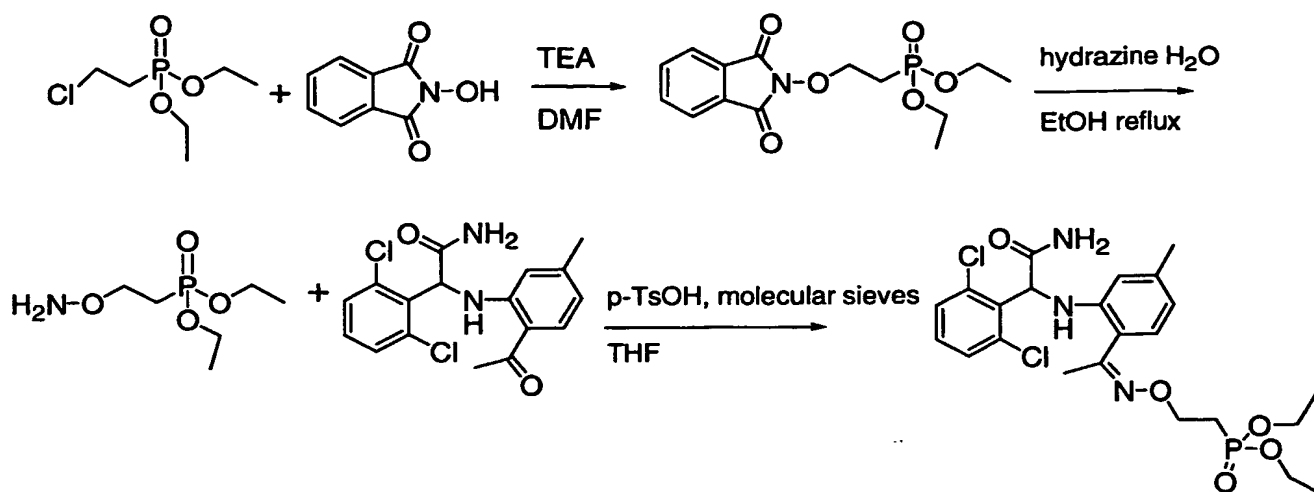
By using a variation of the benzaldehyde shown as compound 1 in Scheme 1, further points of attachment are also attainable. By using, for example, 2,6-dichloro (3,4, or 5 nitro) benzaldehyde, and following Scheme 1, the PO(R$_1$)(R$_2$) is attached at any position of the ring which starts out as the benzaldehyde. Further examples of compounds that can be made in this way are compounds 11, 12 and 13 below.

11

12

13
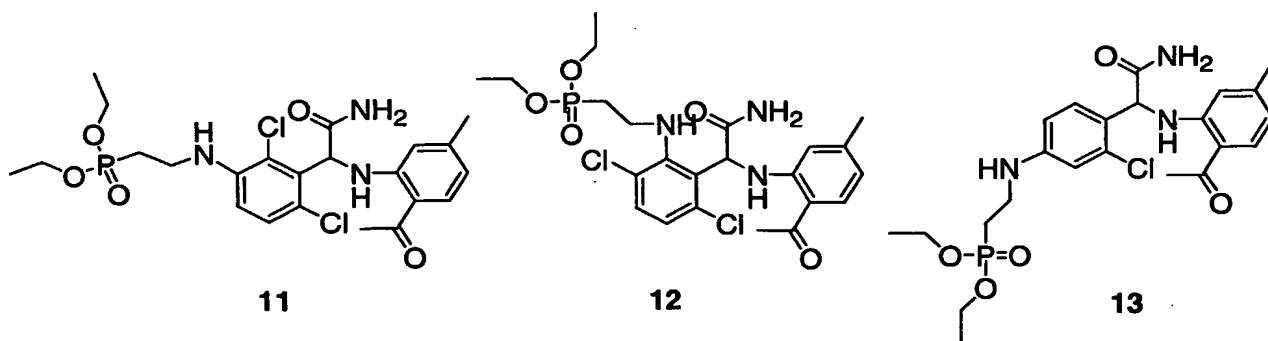
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Scheme General Section

General aspects of these exemplary methods are described below and in the Example. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

5   The terms "treated", "treating", "treatment", and the like, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting

10   compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two.

"Treating" indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M),

15   temperatures (-100°C to 250°C, typically -78°C to 150°C, more typically -78°C to 100°C, still more typically 0°C to 100°C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis is used in selecting the

20   conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes above and in the examples (hereafter

25   "exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step

30   or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example, size exclusion or ion exchange chromatography, high, medium, or

35   low pressure liquid chromatography, small scale and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent

270

selected to bind to or render otherwise separable a desired product, unreacted starting
material, reaction by product, or the like. Such reagents include adsorbents or absorbents
such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively,
the reagents can be acids in the case of a basic material, bases in the case of an acidic

5   material, binding reagents such as antibodies, binding proteins, selective chelators such as
crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials
involved. For example, boiling point, and molecular weight in distillation and sublimation,
presence or absence of polar functional groups in chromatography, stability of materials in

10   acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply
techniques most likely to achieve the desired separation.

All literature and patent citations above are hereby expressly incorporated by
reference at the locations of their citation. Specifically cited sections or pages of the above
cited works are incorporated by reference with specificity. The invention has been described

15   in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter
of the following Embodiments. It is apparent that certain modifications of the methods and
compositions of the following Embodiments can be made within the scope and spirit of the
invention.

Scheme 1001

R-link—P(=O)(OR^1)—OR^1 **27.1** —1→ R-link—P(=O)(OR^1)—OH **27.2**

R-link—P(=O)(OR^1)—OR^1 **27.1** —2→ R-link—P(=O)(OH)—OH **27.3**

R-link—P(=O)(OR^1)—OH **27.2** —3→ R-link—P(=O)(OH)—OH **27.3**

R-link—P(=O)(OR^1)—OH **27.2** —4→ R-link—P(=O)(OR^1)—OR^1 **27.1**

R-link—P(=O)(OH)—OH **27.3** —5→ R-link—P(=O)(OR^1)—OH **27.2**

R-link—P(=O)(OH)—OH **27.3** —6→ R-link—P(=O)(OR^1)—OR^1 **27.1**
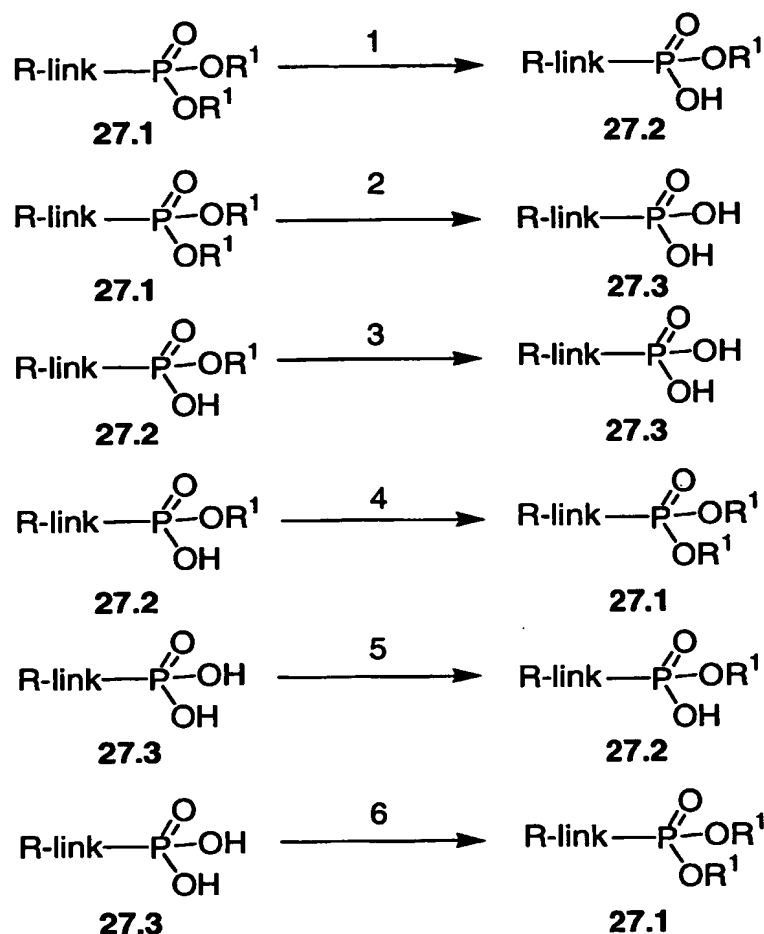
Scheme 1001 shows the interconversions of certain phosphonate compounds: acids –

5   P(O)(OH)$_2$; mono-esters -P(O)(OR$_1$)(OH); and diesters -P(O)(OR$_1$)$_2$ in which the R^1 groups

are independently selected, and defined herein before, and the phosphorus is attached through

a carbon moiety (link, i.e. linker), which is attached to the rest of the molecule, e.g. drug or

drug intermediate (R). The R^1 groups attached to the phosphonate esters in Scheme 1001

may be changed using established chemical transformations. The interconversions may be

10   carried out in the precursor compounds or the final products using the methods described

below. The methods employed for a given phosphonate transformation depend on the nature

of the substituent R^1. The preparation and hydrolysis of phosphonate esters is described in

Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester **27.1** into the corresponding phosphonate

15   monoester **27.2** (Scheme 1001, Reaction 1) can be accomplished by a number of methods.

For example, the ester **27.1** in which R^1 is an arylalkyl group such as benzyl, can be converted into the monoester compound **27.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in *J. Org. Chem.*, 1995, 60:2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about

5   110°C. The conversion of the diester **27.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **27.2** can be effected by treatment of the ester **27.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **27.2** in which one of the groups R^1 is arylalkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters **27.2** in

10   which R^1 is alkyl, by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, can be converted into the monoester **27.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure

15   described in *J. Org. Chem.*, 38:3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **27.1** or a phosphonate monoester **27.2** into the corresponding phosphonic acid **27.3** (Scheme 1001, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in *J. Chem. Soc., Chem. Comm.*, 739, 1979. The reaction is conducted in an inert solvent such as, for

20   example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **27.2** in which R^1 is arylalkyl such as benzyl, can be converted into the corresponding phosphonic acid **27.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxane. A phosphonate monoester **27.2** in which R^1 is alkenyl

25   such as, for example, allyl, can be converted into the phosphonic acid **27.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68:618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **27.1** in which R^1 is benzyl is described in *J. Org. Chem.*, 24:434, 1959. Platinum-catalyzed hydrogenolysis of

30   phosphonate esters **27.1** in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, 78:2336, 1956.

The conversion of a phosphonate monoester **27.2** into a phosphonate diester **27.1** (Scheme 1001, Reaction 4) in which the newly introduced R^1 group is alkyl, arylalkyl, or

haloalkyl such as chloroethyl, can be effected by a number of reactions in which the substrate
27.2 is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent.
Suitable coupling agents are those employed for the preparation of carboxylate esters, and
include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is

5   preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-
yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the
reaction is performed in a polar solvent such as dimethylformamide, in the presence of a
tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case
the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl

10   phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate
monoester 27.1 to the diester 27.1 can be effected by the use of the Mitsunobu reaction. The
substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl
azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the
phosphonate monoester 27.2 can be transformed into the phosphonate diester 27.1, in which

15   the introduced R^1 group is alkenyl or arylalkyl, by reaction of the monoester with the halide
R^1Br, in which R^1 is as alkenyl or arylalkyl. The alkylation reaction is conducted in a polar
organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as
cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the
phosphonate diester in a two step procedure. In the first step, the phosphonate monoester

20   27.2 is transformed into the chloro analog $-P(O)(OR^1)Cl$ by reaction with thionyl chloride or
oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M.
Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $-P(O)(OR^1)Cl$ is
then reacted with the hydroxy compound R^1OH, in the presence of a base such as
triethylamine, to afford the phosphonate diester 27.1.

25   A phosphonic acid $-P(O)(OH)_2$ can be transformed into a phosphonate monoester
$-P(O)(OR^1)(OH)$ (Scheme 1001, Reaction 5) by means of the methods described above of for
the preparation of the phosphonate diester $-P(O)(OR^1)_2$ 27.1, except that only one molar
proportion of the component R^1OH or R^1Br is employed.

          A phosphonic acid $-P(O)(OH)_2$ 27.3 can be transformed into a phosphonate diester

30    $-P(O)(OR^1)_2$ 27.1 (Scheme 1, Reaction 6) by a coupling reaction with the hydroxy compound
R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and
triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine.
Alternatively, phosphonic acids 27.3 can be transformed into phosphonic esters 27.1 in which

R^1 is aryl, such as phenyl, by means of a coupling reaction employing, for example, phenol and dicyclohexylcarbodiimide in pyridine at about 70°C. Alternatively, phosphonic acids 27.3 can be transformed into phosphonic esters 27.1 in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, in the presence of a base such as cesium carbonate, to afford the phosphonic ester 27.1.

Amino alkyl phosphonate compounds 809:

809
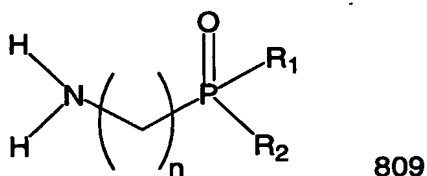
are a generic representative of compounds 811, 813, 814, 816 and 818. Some methods to prepare embodiments of 809 are shown in Scheme 1002. Commercial amino phosphonic acid 810 was protected as carbamate 811. The phosphonic acid 811 was converted to phosphonate 812 upon treatment with ROH in the presence of DCC or other conventional coupling reagents. Coupling of phosphonic acid 811 with esters of amino acid 820 provided bisamidate 817. Conversion of acid 811 to bisphenyl phosphonate followed by hydrolysis gave mono-phosphonic acid 814 (Cbz = $C_6H_5CH_2C(O)-$), which was then transformed to mono-phosphonic amidate 815. Carbamates 813, 816 and 818 were converted to their corresponding amines upon hydrogenation. Compounds 811, 813, 814, 816 and 818 are useful intermediates to form the phosphonate compounds of the invention.

Preparation of carboalkoxy-substituted phosphonate bisamidates, monoamidates, diesters and monoesters.

A number of methods are available for the conversion of phosphonic acids into amidates and esters. In one group of methods, the phosphonic acid is either converted into an isolated activated intermediate such as a phosphoryl chloride, or the phosphonic acid is activated in situ for reaction with an amine or a hydroxy compound.

The conversion of phosphonic acids into phosphoryl chlorides is accomplished by reaction with thionyl chloride, for example as described in J. Gen. Chem. USSR, 1983, 53, 480, Zh. Obschei Khim., 1958, 28, 1063, or J. Org. Chem., 1994, 59, 6144, or by reaction with oxalyl chloride, as described in J. Am. Chem. Soc., 1994, 116, 3251, or J. Org. Chem., 1994, 59,

5   6144, or by reaction with phosphorus pentachloride, as described in J. Org. Chem., 2001, 66, 329, or in J. Med. Chem., 1995, 38, 1372. The resultant phosphoryl chlorides are then reacted with amines or hydroxy compounds in the presence of a base to afford the amidate or ester products.

10   Phosphonic acids are converted into activated imidazolyl derivatives by reaction with carbonyl diimidazole, as described in J. Chem. Soc., Chem. Comm., 1991, 312, or Nucleosides Nucleotides 2000, 19, 1885. Activated sulfonyloxy derivatives are obtained by the reaction of phosphonic acids with trichloromethylsulfonyl chloride, as described in J. Med. Chem. 1995, 38, 4958, or with triisopropylbenzenesulfonyl chloride, as described in

15   Tet. Lett., 1996, 7857, or Bioorg. Med. Chem. Lett., 1998, 8, 663. The activated sulfonyloxy derivatives are then reacted with amines or hydroxy compounds to afford amidates or esters. Alternatively, the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a diimide coupling agent. The preparation of phosphonic amidates and esters by means of coupling reactions in the presence of dicyclohexyl carbodiimide is described, for

20   example, in J. Chem. Soc., Chem. Comm., 1991, 312, or J. Med. Chem., 1980, 23, 1299 or Coll. Czech. Chem. Comm., 1987, 52, 2792. The use of ethyl dimethylaminopropyl carbodiimide for activation and coupling of phosphonic acids is described in Tet. Lett., 2001, 42, 8841, or Nucleosides Nucleotides, 2000, 19, 1885.

25   A number of additional coupling reagents have been described for the preparation of amidates and esters from phosphonic acids. The agents include Aldrithiol-2, and PYBOP and BOP, as described in J. Org. Chem., 1995, 60, 5214, and J. Med. Chem., 1997, 40, 3842, mesitylene-2-sulfonyl-3-nitro-1,2,4-triazole (MSNT), as described in J. Med. Chem., 1996, 39, 4958, diphenylphosphoryl azide, as described in J. Org. Chem., 1984, 49, 1158, 1-(2,4,6-

30   triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole (TPSNT) as described in Bioorg. Med. Chem. Lett., 1998, 8, 1013, bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP), as described in Tet. Lett., 1996, 37, 3997, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-

dioxaphosphinane, as described in Nucleosides Nucleotides 1995, 14, 871, and diphenyl
chlorophosphate, as described in J. Med. Chem., 1988, 31, 1305.

Phosphonic acids are converted into amidates and esters by means of the Mitsonobu reaction,
5   in which the phosphonic acid and the amine or hydroxy reactant are combined in the presence
of a triaryl phosphine and a dialkyl azodicarboxylate. The procedure is described in Org.
Lett., 2001, 3, 643, or J. Med. Chem., 1997, 40, 3842.

Phosphonic esters are also obtained by the reaction between phosphonic acids and halo
10   compounds, in the presence of a suitable base. The method is described, for example, in
Anal. Chem., 1987, 59, 1056, or J. Chem. Soc. Perkin Trans., I, 1993, 19, 2303, or J. Med.
Chem., 1995, 38, 1372, or Tet. Lett., 2002, 43, 1161.

Schemes 1 - 4 illustrate the conversion of phosphonate esters and phosphonic acids into
15   carboalkoxy-substituted phosphorobisamidates (Scheme 1), phosphoroamidates (Scheme 2),
phosphonate monoesters (Scheme 3) and phosphonate diesters, (Scheme 4).

Scheme 1 illustrates various methods for the conversion of phosphonate diesters **1.1** into
phosphorobisamidates **1.5**. The diester **1.1**, prepared as described previously, is hydrolyzed,
20   either to the monoester **1.2** or to the phosphonic acid **1.6**. The methods employed for these
transformations are described above. The monoester **1.2** is converted into the monoamidate
1.3 by reaction with an aminoester **1.9**, in which the group R^2 is H or alkyl, the group R^4 is an
alkylene moiety such as, for example, $CHCH_3$, $CHPr^1$, $CH(CH_2Ph)$, $CH_2CH(CH_3)$ and the
like, or a group present in natural or modified aminoacids, and the group R^5 is alkyl. The
25   reactants are combined in the presence of a coupling agent such as a carbodiimide, for
example dicyclohexyl carbodiimide, as described in J. Am. Chem. Soc., 1957, 79, 3575,
optionally in the presence of an activating agent such as hydroxybenztriazole, to yield the
amidate product **1.3**. The amidate-forming reaction is also effected in the presence of
coupling agents such as BOP, as described in J. Org. Chem., 1995, 60, 5214, Aldrithiol,
30   PYBOP and similar coupling agents used for the preparation of amides and esters.
Alternatively, the reactants **1.2** and **1.9** are transformed into the monoamidate **1.3** by means
of a Mitsonobu reaction. The preparation of amidates by means of the Mitsonobu reaction is
described in J. Med. Chem., 1995, 38, 2742. Equimolar amounts of the reactants are

combined in an inert solvent such as tetrahydrofuran in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The thus-obtained monoamidate ester 1.3 is then transformed into amidate phosphonic acid 1.4. The conditions used for the hydrolysis reaction depend on the nature of the R^1 group, as described previously. The phosphonic acid amidate 1.4 is then
5   reacted with an aminoester 1.9, as described above, to yield the bisamidate product 1.5, in which the amino substituents are the same or different.

An example of this procedure is shown in Scheme 1, Example 1. In this procedure, a dibenzyl phosphonate 1.14 is reacted with diazabicyclooctane (DABCO) in toluene at reflux,
10 as described in J. Org. Chem., 1995, 60, 2946, to afford the monobenzyl phosphonate 1.15. The product is then reacted with equimolar amounts of ethyl alaninate 1.16 and dicyclohexyl carbodiimide in pyridine, to yield the amidate product 1.17. The benzyl group is then removed, for example by hydrogenolysis over a palladium catalyst, to give the monoacid product 1.18. This compound is then reacted in a Mitsonobu reaction with ethyl leucinate
15 1.19, triphenyl phosphine and diethylazodicarboxylate, as described in J. Med. Chem., 1995, 38, 2742, to produce the bisamidate product 1.20.

Using the above procedures, but employing, in place of ethyl leucinate 1.19 or ethyl alaninate 1.16, different aminoesters 1.9, the corresponding products 1.5 are obtained.
20
Alternatively, the phosphonic acid 1.6 is converted into the bisamidate 1.5 by use of the coupling reactions described above. The reaction is performed in one step, in which case the nitrogen-related substituents present in the product 1.5 are the same, or in two steps, in which case the nitrogen-related substituents can be different.
25 An example of the method is shown in Scheme 1, Example 2. In this procedure, a phosphonic acid 1.6 is reacted in pyridine solution with excess ethyl phenylalaninate 1.21 and dicyclohexylcarbodiimide, for example as described in J. Chem. Soc., Chem. Comm., 1991, 1063, to give the bisamidate product 1.22.

30 Using the above procedures, but employing, in place of ethyl phenylalaninate, different aminoesters 1.9, the corresponding products 1.5 are obtained.

As a further alternative, the phosphonic acid **1.6** is converted into the mono or bis-activated derivative **1.7**, in which Lv is a leaving group such as chloro, imidazolyl, triisopropylbenzenesulfonyloxy etc. The conversion of phosphonic acids into chlorides **1.7** (Lv = Cl) is effected by reaction with thionyl chloride or oxalyl chloride and the like, as

5   described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17. The conversion of phosphonic acids into monoimidazolides **1.7** (Lv = imidazolyl) is described in J. Med. Chem., 2002, 45, 1284 and in J. Chem. Soc. Chem. Comm., 1991, 312. Alternatively, the phosphonic acid is activated by reaction with triisopropylbenzenesulfonyl chloride, as described in Nucleosides and Nucleotides, 2000, 10, 1885. The activated product

10   is then reacted with the aminoester **1.9**, in the presence of a base, to give the bisamidate **1.5**. The reaction is performed in one step, in which case the nitrogen substituents present in the product **1.5** are the same, or in two steps, via the intermediate **1.11**, in which case the nitrogen substituents can be different.

15   Examples of these methods are shown in Scheme 1, Examples 3 and 5. In the procedure illustrated in Scheme 1, Example 3, a phosphonic acid **1.6** is reacted with ten molar equivalents of thionyl chloride, as described in Zh. Obschei Khim., 1958, 28, 1063, to give the dichloro compound **1.23**. The product is then reacted at reflux temperature in a polar aprotic solvent such as acetonitrile, and in the presence of a base such as triethylamine, with

20   butyl serinate **1.24** to afford the bisamidate product **1.25**.

Using the above procedures, but employing, in place of butyl serinate **1.24**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

25   In the procedure illustrated in Scheme 1, Example 5, the phosphonic acid **1.6** is reacted, as described in J. Chem. Soc. Chem. Comm., 1991, 312, with carbonyl diimidazole to give the imidazolide **1.32**. The product is then reacted in acetonitrile solution at ambient temperature, with one molar equivalent of ethyl alaninate **1.33** to yield the monodisplacement product **1.34**. The latter compound is then reacted with carbonyl diimidazole to produce the activated

30   intermediate **1.35**, and the product is then reacted, under the same conditions, with ethyl N-methylalaninate **1.33a** to give the bisamidate product **1.36**.

Using the above procedures, but employing, in place of ethyl alaninate **1.33** or ethyl N-methylalaninate **1.33a**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

5   The intermediate monoamidate **1.3** is also prepared from the monoester **1.2** by first converting the monoester into the activated derivative **1.8** in which Lv is a leaving group such as halo, imidazolyl etc, using the procedures described above. The product **1.8** is then reacted with an aminoester **1.9** in the presence of a base such as pyridine, to give an intermediate monoamidate product **1.3**. The latter compound is then converted, by removal

10   of the R^1 group and coupling of the product with the aminoester **1.9**, as described above, into the bisamidate **1.5**.

An example of this procedure, in which the phosphonic acid is activated by conversion to the chloro derivative **1.26**, is shown in Scheme 1, Example 4. In this procedure, the phosphonic

15   monobenzyl ester **1.15** is reacted, in dichloromethane, with thionyl chloride, as described in Tet. Let., 1994, 35, 4097, to afford the phosphoryl chloride **1.26**. The product is then reacted in acetonitrile solution at ambient temperature with one molar equivalent of ethyl 3-amino-2-methylpropionate **1.27** to yield the monoamidate product **1.28**. The latter compound is hydrogenated in ethyl acetate over a 5% palladium on carbon catalyst to produce the

20   monoacid product **1.29**. The product is subjected to a Mitsonobu coupling procedure, with equimolar amounts of butyl alaninate **1.30**, triphenyl phosphine, diethylazodicarboxylate and triethylamine in tetrahydrofuran, to give the bisamidate product **1.31**.

Using the above procedures, but employing, in place of ethyl 3-amino-2-methylpropionate

25   **1.27** or butyl alaninate **1.30**, different aminoesters **1.9**, the corresponding products **1.5** are obtained.

The activated phosphonic acid derivative **1.7** is also converted into the bisamidate **1.5** via the diamino compound **1.10**. The conversion of activated phosphonic acid derivatives such as

30   phosphoryl chlorides into the corresponding amino analogs **1.10**, by reaction with ammonia, is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976. The diamino compound **1.10** is then reacted at elevated temperature with a haloester

280

1.12, in a polar organic solvent such as dimethylformamide, in the presence of a base such as

dimethylaminopyridine or potassium carbonate, to yield the bisamidate **1.5**.

An example of this procedure is shown in Scheme 1, Example **6**. In this method, a

dichlorophosphonate **1.23** is reacted with ammonia to afford the diamide **1.37**. The reaction

5   is performed in aqueous, aqueous alcoholic or alcoholic solution, at reflux temperature. The

resulting diamino compound is then reacted with two molar equivalents of ethyl 2-bromo-3-

methylbutyrate **1.38**, in a polar organic solvent such as N-methylpyrrolidinone at ca. 150°C,

in the presence of a base such as potassium carbonate, and optionally in the presence of a

catalytic amount of potassium iodide, to afford the bisamidate product **1.39**.

10

Using the above procedures, but employing, in place of ethyl 2-bromo-3-methylbutyrate **1.38**,

different haloesters **1.12** the corresponding products **1.5** are obtained.

The procedures shown in Scheme 1 are also applicable to the preparation of bisamidates in

15   which the aminoester moiety incorporates different functional groups. Scheme 1, Example **7**

illustrates the preparation of bisamidates derived from tyrosine. In this procedure, the

monoimidazolide **1.32** is reacted with propyl tyrosinate **1.40**, as described in Example **5**, to

yield the monoamidate **1.41**. The product is reacted with carbonyl diimidazole to give the

imidazolide **1.42**, and this material is reacted with a further molar equivalent of propyl

20   tyrosinate to produce the bisamidate product **1.43**.

Using the above procedures, but employing, in place of propyl tyrosinate **1.40**, different

aminoesters **1.9**, the corresponding products **1.5** are obtained. The aminoesters employed in

the two stages of the above procedure can be the same or different, so that bisamidates with

25   the same or different amino substituents are prepared.

Scheme 2 illustrates methods for the preparation of phosphonate monoamidates.

In one procedure, a phosphonate monoester **1.1** is converted, as described in Scheme 1, into

the activated derivative **1.8**. This compound is then reacted, as described above, with an

30   aminoester **1.9**, in the presence of a base, to afford the monoamidate product **2.1**.

The procedure is illustrated in Scheme 2, Example **1**. In this method, a monophenyl

phosphonate **2.7** is reacted with, for example, thionyl chloride, as described in J. Gen. Chem.

USSR., 1983, 32, 367, to give the chloro product **2.8**. The product is then reacted, as described in Scheme **1**, with ethyl alaninate **2.9**, to yield the amidate **2.10**.

Using the above procedures, but employing, in place of ethyl alaninate **2.9**, different

5   aminoesters **1.9**, the corresponding products **2.1** are obtained.

Alternatively, the phosphonate monoester **1.1** is coupled, as described in Scheme **1**, with an aminoester **1.9** to produce the amidate **2.1**. If necessary, the R^1 substituent is then altered, by initial cleavage to afford the phosphonic acid **2.2**. The procedures for this transformation

10   depend on the nature of the R^1 group, and are described above. The phosphonic acid is then transformed into the ester amidate product **2.3**, by reaction with the hydroxy compound R^3OH, in which the group R^3 is aryl, heteroaryl, alkyl, cycloalkyl, haloalkyl etc, using the same coupling procedures (carbodiimide, Aldrithiol-2, PYBOP, Mitsonobu reaction etc) described in Scheme **1** for the coupling of amines and phosphonic acids.

Scheme 1

$\text{R-link}-\overset{O}{\underset{\underset{(R^4)}{|}}{\overset{||}{P}}}-\overset{NH}{\underset{CO_2R^5}{|}}NH(R^4)CO_2R^5$ **1.5**

$\xleftarrow[\text{1.12}]{\text{Ha}(R^4)CO_2R^5}$

$\text{R-link}-\overset{O}{\overset{||}{P}}-NH_2$ (NH_2) **1.10** Ex6

$\xleftarrow{}$ $\text{R-link}-\overset{O}{\overset{||}{P}}-Lv$ (Lv or OH) **1.7**

$\xrightarrow{\text{1.9}}$ $\text{R-link}-\overset{O}{\overset{||}{P}}-N\overset{R^2}{\underset{(R^4)}{}}$ (Lv or OH) CO_2R^5 **1.11**

$\xrightarrow{\text{1.9}}$

$\text{R-link}-\overset{O}{\overset{||}{P}}-OR^1$ (OR^1) **1.1** $\rightarrow$ $\text{R-link}-\overset{O}{\overset{||}{P}}-OR^1$ (OH) **1.2** $\rightarrow$ $\text{R-link}-\overset{O}{\overset{||}{P}}-OH$ (OH) **1.6** $\rightarrow$ $\text{R-link}-\overset{O}{\overset{||}{P}}-N\overset{R^2}{\underset{(R^4)}{}}(R^4)CO_2R^5$ $N\overset{R^2}{\underset{CO_2R^5}{}}$ **1.5**

$\text{R-link}-\overset{O}{\overset{||}{P}}-OR^1$ (Lv) **1.8**

$\xrightarrow[R^2NH(R^4)CO_2R^5 \quad \text{1.9}]{}$

$\text{R-link}-\overset{O}{\overset{||}{P}}-OR^1$ $N-R^2$ (R^4) CO_2R^5 **1.3** $\rightarrow$

$\text{R-link}-\overset{O}{\overset{||}{P}}-OH$ $N-R^2$ (R^4) CO_2R^5 **1.4**

$\xrightarrow{\text{1.9}}$ **1.5**

Scheme 1 Example 1

$\text{R-link}-\overset{O}{\overset{||}{P}}-OBn$ (OBn) **1.14** $\rightarrow$ $\text{R-link}-\overset{O}{\overset{||}{P}}-OH$ (OBn) **1.15**

$\xrightarrow[\text{1.16}]{H_2NCH(Me)CO_2Et}$

$\text{R-link}-\overset{O}{\overset{||}{P}}-N\overset{H}{\underset{COOEt}{}}\overset{Me}{}$ (OBn) **1.17** $\rightarrow$ $\text{R-link}-\overset{O}{\overset{||}{P}}-N\overset{H}{\underset{COOEt}{}}\overset{Me}{}$ (OH) **1.18**

$\xrightarrow[\text{1.19}]{H_2NCH(CH_2Pr^i)CO_2Et}$

$\text{R-link}-\overset{O}{\overset{||}{P}}-N\overset{H}{\underset{}{}}\overset{Me}{\underset{COOEt}{}}$ $\overset{NH}{\underset{Pr^iH_2C}{}}\overset{}{\underset{COOEt}{}}$ **1.20**

Scheme 1 Example 2

$\text{R-link}-\overset{O}{\overset{||}{P}}-OH$ (OH) **1.6**

$\xrightarrow[\text{1.21}]{H_2NCH(Bn)CO_2Et}$

$\text{R-link}-\overset{O}{\overset{||}{P}}-\overset{Bn}{\underset{NH}{\overset{}{\underset{COOEt}{}}}}\overset{COOEt}{}$ $\overset{NH}{\underset{Bn}{\underset{COOEt}{}}}$ **1.22**

Scheme 1 Example 3

Scheme 1 Example 4

Scheme 1 Example 5

Scheme 1 Example 6

Scheme 1 Example 7

Examples of this method are shown in Scheme 2, Examples and 2 and 3. In the sequence shown in Example 2, a monobenzyl phosphonate **2.11** is transformed by reaction with ethyl

5 alaninate, using one of the methods described above, into the monoamidate **2.12**. The benzyl group is then removed by catalytic hydrogenation in ethyl acetate solution over a 5% palladium on carbon catalyst, to afford the phosphonic acid amidate **2.13**. The product is then reacted in dichloromethane solution at ambient temperature with equimolar amounts of 1-(dimethylaminopropyl)-3-ethylcarbodiimide and trifluoroethanol **2.14**, for example as

10 described in Tet. Lett., 2001, 42, 8841, to yield the amidate ester **2.15**.

In the sequence shown in Scheme 2, Example 3, the monoamidate **2.13** is coupled, in tetrahydrofuran solution at ambient temperature, with equimolar amounts of dicyclohexyl carbodiimide and 4-hydroxy-N-methylpiperidine **2.16**, to produce the amidate ester product

15 **2.17**.

Using the above procedures, but employing, in place of the ethyl alaninate product **2.12** different monoacids **2.2**, and in place of trifluoroethanol **2.14** or 4-hydroxy-N-methylpiperidine **2.16**, different hydroxy compounds R^3OH, the corresponding products **2.3**

20 are obtained.

Alternatively, the activated phosphonate ester **1.8** is reacted with ammonia to yield the amidate **2.4**. The product is then reacted, as described in Scheme 1, with a haloester **2.5**, in the presence of a base, to produce the amidate product **2.6**. If appropriate, the nature of the

25 R^1 group is changed, using the procedures described above, to give the product **2.3**. The method is illustrated in Scheme 2, Example 4. In this sequence, the monophenyl phosphoryl

chloride **2.18** is reacted, as described in Scheme **1**, with ammonia, to yield the amino product **2.19**. This material is then reacted in N-methylpyrrolidinone solution at 170°C with butyl 2-bromo-3-phenylpropionate **2.20** and potassium carbonate, to afford the amidate product **2.21**. Using these procedures, but employing, in place of butyl 2-bromo-3-phenylpropionate **2.20**,

5   different haloesters **2.5**, the corresponding products **2.6** are obtained.

The monoamidate products **2.3** are also prepared from the doubly activated phosphonate derivatives **1.7**. In this procedure, examples of which are described in Synlett., 1998, 1, 73, the intermediate **1.7** is reacted with a limited amount of the aminoester **1.9** to give the mono-

10   displacement product **1.11**. The latter compound is then reacted with the hydroxy compound R^{3}OH in a polar organic solvent such as dimethylformamide, in the presence of a base such as diisopropylethylamine, to yield the monoamidate ester **2.3**.

The method is illustrated in Scheme 2, Example 5. In this method, the phosphoryl dichloride

15   **2.22** is reacted in dichloromethane solution with one molar equivalent of ethyl N-methyl tyrosinate **2.23** and dimethylaminopyridine, to generate the monoamidate **2.24**. The product is then reacted with phenol **2.25** in dimethylformamide containing potassium carbonate, to yield the ester amidate product **2.26**.

20   Using these procedures, but employing, in place of ethyl N-methyl tyrosinate **2.23** or phenol **2.25**, the aminoesters **1.9** and/or the hydroxy compounds R^{3}OH, the corresponding products **2.3** are obtained.

Scheme 2

Scheme 2 Example 1

Scheme 2 Example 2

Scheme 2 Example 3

Scheme 2 Example 4

R-link—$\overset{\overset{\displaystyle O}{\|}}{\underset{\displaystyle Cl}{P}}$—OPh   ⟶   R-link—$\overset{\overset{\displaystyle O}{\|}}{\underset{\displaystyle NH_2}{P}}$—OPh $\xrightarrow{\text{BrCH(Bn)CO}_2\text{Bu}}{\textbf{2.20}}$ R-link—$\overset{\overset{\displaystyle O}{\|}}{\underset{\displaystyle NH}{P}}$—OPh

           Bn—$\underset{CO_2Bu}{\big|}$

2.18   **2.19**   **2.21**

Scheme 2 Example 5

R-link—$\overset{\overset{\displaystyle O}{\|}}{\underset{\displaystyle Cl}{P}}$—Cl $\xrightarrow{\quad\textbf{2.23}\quad}$ R-link—$\overset{\overset{\displaystyle O}{\|}}{P}$—Cl $\xrightarrow[\textbf{2.25}]{\text{PhOH}}$ R-link—$\overset{\overset{\displaystyle O}{\|}}{P}$—O—

2.22   **2.24**   **2.26**

Scheme 3 illustrates methods for the preparation of carboalkoxy-substituted phosphonate diesters in which one of the ester groups incorporates a carboalkoxy substituent.

5   In one procedure, a phosphonate monoester **1.1**, prepared as described above, is coupled, using one of the methods described above, with a hydroxyester **3.1**, in which the groups R^4 and R^5 are as described in Scheme 1. For example, equimolar amounts of the reactants are coupled in the presence of a carbodiimide such as dicyclohexyl carbodiimide, as described in Aust. J. Chem., 1963, 609, optionally in the presence of dimethylaminopyridine, as described

10   in Tet., 1999, 55, 12997. The reaction is conducted in an inert solvent at ambient temperature.

The procedure is illustrated in Scheme 3, Example 1. In this method, a monophenyl phosphonate **3.9** is coupled, in dichloromethane solution in the presence of dicyclohexyl

15   carbodiimide, with ethyl 3-hydroxy-2-methylpropionate **3.10** to yield the phosphonate mixed diester **3.11**.

Using this procedure, but employing, in place of ethyl 3-hydroxy-2-methylpropionate **3.10**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

20

The conversion of a phosphonate monoester **1.1** into a mixed diester **3.2** is also accomplished by means of a Mitsonobu coupling reaction with the hydroxyester **3.1**, as described in Org. Lett., 2001, 643. In this method, the reactants **1.1** and **3.1** are combined in a polar solvent such as tetrahydrofuran, in the presence of a triarylphosphine and a dialkyl azodicarboxylate,

5   to give the mixed diester **3.2**. The R^1 substituent is varied by cleavage, using the methods described previously, to afford the monoacid product **3.3**. The product is then coupled, for example using methods described above, with the hydroxy compound R^3OH, to give the diester product **3.4**.

10   The procedure is illustrated in Scheme 3, Example 2. In this method, a monoallyl phosphonate **3.12** is coupled in tetrahydrofuran solution, in the presence of triphenylphosphine and diethylazodicarboxylate, with ethyl lactate **3.13** to give the mixed diester **3.14**. The product is reacted with tris(triphenylphosphine) rhodium chloride (Wilkinson catalyst) in acetonitrile, as described previously, to remove the allyl group and

15   produce the monoacid product **3.15**. The latter compound is then coupled, in pyridine solution at ambient temperature, in the presence of dicyclohexyl carbodiimide, with one molar equivalent of 3-hydroxypyridine **3.16** to yield the mixed diester **3.17**.

Using the above procedures, but employing, in place of the ethyl lactate **3.13** or 3-

20   hydroxypyridine, a different hydroxyester **3.1** and/or a different hydroxy compound R^3OH, the corresponding products **3.4** are obtained.

The mixed diesters **3.2** are also obtained from the monoesters **1.1** via the intermediacy of the activated monoesters **3.5**. In this procedure, the monoester **1.1** is converted into the activated

25   compound **3.5** by reaction with, for example, phosphorus pentachloride, as described in J. Org. Chem., 2001, 66, 329, or with thionyl chloride or oxalyl chloride (Lv = Cl), or with triisopropylbenzenesulfonyl chloride in pyridine, as described in Nucleosides and Nucleotides, 2000, 19, 1885, or with carbonyl diimidazole, as described in J. Med. Chem., 2002, 45, 1284. The resultant activated monoester is then reacted with the hydroxyester **3.1**,

30   as described above, to yield the mixed diester **3.2**.

The procedure is illustrated in Scheme 3, Example 3. In this sequence, a monophenyl phosphonate **3.9** is reacted, in acetonitrile solution at 70°C, with ten equivalents of thionyl

chloride, so as to produce the phosphoryl chloride **3.19**. The product is then reacted with ethyl 4-carbamoyl-2-hydroxybutyrate **3.20** in dichloromethane containing triethylamine, to give the mixed diester **3.21**.

5   Using the above procedures, but employing, in place of ethyl 4-carbamoyl-2-hydroxybutyrate ·**3.20**, different hydroxyesters **3.1**, the corresponding products **3.2** are obtained.

The mixed phosphonate diesters are also obtained by an alternative route for incorporation of the R^3O group into intermediates **3.3** in which the hydroxyester moiety is already

10   incorporated. In this procedure, the monoacid intermediate **3.3** is converted into the activated derivative **3.6** in which Lv is a leaving group such as chloro, imidazole, and the like, as previously described. The activated intermediate is then reacted with the hydroxy compound R^3OH, in the presence of a base, to yield the mixed diester product **3.4**.

15   The method is illustrated in Scheme 3, Example 4. In this sequence, the phosphonate monoacid **3.22** is reacted with trichloromethanesulfonyl chloride in tetrahydrofuran containing collidine, as described in J. Med. Chem., 1995, 38, 4648, to produce the trichloromethanesulfonyloxy product **3.23**. This compound is reacted with 3-(morpholinomethyl)phenol **3.24** in dichloromethane containing triethylamine, to yield the

20   mixed diester product **3.25**.

Using the above procedures, but employing, in place of with 3-(morpholinomethyl)phenol **3.24**, different carbinols R^3OH, the corresponding products **3.4** are obtained.

25   The phosphonate esters **3.4** are also obtained by means of alkylation reactions performed on the monoesters **1.1**. The reaction between the monoacid **1.1** and the haloester **3.7** is performed in a polar solvent in the presence of a base such as diisopropylethylamine, as described in Anal. Chem., 1987, 59, 1056, or triethylamine, as described in J. Med. Chem., 1995, 38, 1372, or in a non-polar solvent such as benzene, in the presence of 18-crown-6, as

30   described in Syn. Comm., 1995, 25, 3565.

The method is illustrated in Scheme 3, Example 5. In this procedure, the monoacid **3.26** is reacted with ethyl 2-bromo-3-phenylpropionate **3.27** and diisopropylethylamine in dimethylformamide at 80°C to afford the mixed diester product **3.28**.

5   Using the above procedure, but employing, in place of ethyl 2-bromo-3-phenylpropionate **3.27**, different haloesters **3.7**, the corresponding products **3.4** are obtained.

Scheme 3

Scheme 3 Example 1

Scheme 3 Example 2

Scheme 3 Example 3

Scheme 3 Example 4

R-link—P(=O)(OH)—O—Me—CO₂Et → R-link—P(=O)(OSO₂CCl₃)—O—Me—CO₂Et → R-link—P(=O)(O-aryl-CH₂-morpholine)—O—Me—CO₂Et

3.22   **3.23**   **3.25**

3.24

Scheme 3 Example 5

R-link—P(=O)(OH)(OCH₂CF₃) →[BrCH(Bn)CO₂Et, **3.27**]→ R-link—P(=O)(OCH(Bn)CO₂Et)(OCH₂CF₃)

3.26   **3.28**

Scheme 4 illustrates methods for the preparation of phosphonate diesters in which both the

5   ester substituents incorporate carboalkoxy groups.

The compounds are prepared directly or indirectly from the phosphonic acids **1.6**. In one alternative, the phosphonic acid is coupled with the hydroxyester **4.2**, using the conditions described previously in Schemes 1 - 3, such as coupling reactions using dicyclohexyl

10 carbodiimide or similar reagents, or under the conditions of the Mitsonobu reaction, to afford the diester product **4.3** in which the ester substituents are identical.

This method is illustrated in Scheme 4, Example 1. In this procedure, the phosphonic acid **1.6** is reacted with three molar equivalents of butyl lactate **4.5** in the presence of Aldrithiol-2

15 and triphenyl phosphine in pyridine at ca. 70°C, to afford the diester **4.6**.
Using the above procedure, but employing, in place of butyl lactate **4.5**, different hydroxyesters **4.2**, the corresponding products **4.3** are obtained.

Alternatively, the diesters **4.3** are obtained by alkylation of the phosphonic acid **1.6** with a

20 haloester **4.1**. The alkylation reaction is performed as described in Scheme 3 for the preparation of the esters **3.4**.

This method is illustrated in Scheme 4, Example 2. In this procedure, the phosphonic acid
1.6 is reacted with excess ethyl 3-bromo-2-methylpropionate 4.7 and diisopropylethylamine
in dimethylformamide at ca. 80°C, as described in Anal. Chem., 1987, 59, 1056, to produce

5   the diester 4.8.

Using the above procedure, but employing, in place of ethyl 3-bromo-2-methylpropionate
4.7, different haloesters 4.1, the corresponding products 4.3 are obtained.

The diesters 4.3 are also obtained by displacement reactions of activated derivatives 1.7 of

10   the phosphonic acid with the hydroxyesters 4.2. The displacement reaction is performed in a
polar solvent in the presence of a suitable base, as described in Scheme 3. The displacement
reaction is performed in the presence of an excess of the hydroxyester, to afford the diester
product 4.3 in which the ester substituents are identical, or sequentially with limited amounts
of different hydroxyesters, to prepare diesters 4.3 in which the ester substituents are different.

15   The methods are illustrated in Scheme 4, Examples 3 and 4. As shown in Example 3, the
phosphoryl dichloride 2.22 is reacted with three molar equivalents of ethyl 3-hydroxy-2-
(hydroxymethyl)propionate 4.9 in tetrahydrofuran containing potassium carbonate, to obtain
the diester product 4.10.

Using the above procedure, but employing, in place of ethyl 3-hydroxy-2-

20   (hydroxymethyl)propionate 4.9, different hydroxyesters 4.2, the corresponding products 4.3
are obtained.

Scheme 4, Example 4 depicts the displacement reaction between equimolar amounts of the
phosphoryl dichloride 2.22 and ethyl 2-methyl-3-hydroxypropionate 4.11, to yield the
monoester product 4.12. The reaction is conducted in acetonitrile at 70°C in the presence of

25   diisopropylethylamine. The product 4.12 is then reacted, under the same conditions, with one
molar equivalent of ethyl lactate 4.13, to give the diester product 4.14.

Using the above procedures, but employing, in place of ethyl 2-methyl-3-hydroxypropionate
4.11 and ethyl lactate 4.13, sequential reactions with different hydroxyesters 4.2, the
corresponding products 4.3 are obtained.

Scheme 4
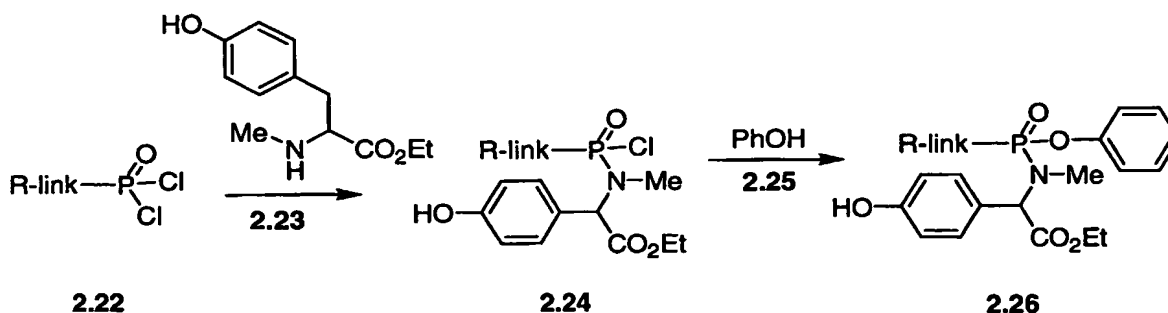

Scheme 4 Example 1

Scheme 4 Example 2

Scheme 4 Example 3

Scheme 4 Example 4

Scheme 1002
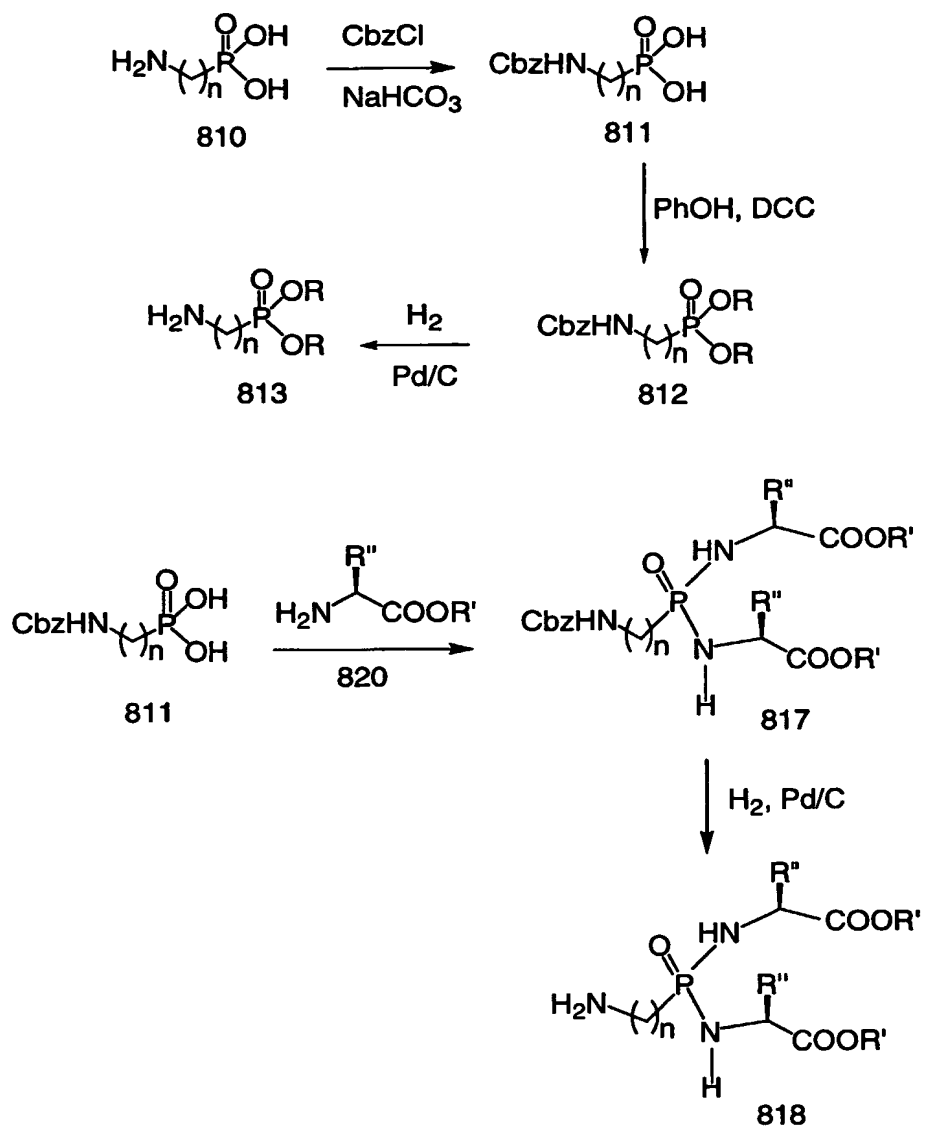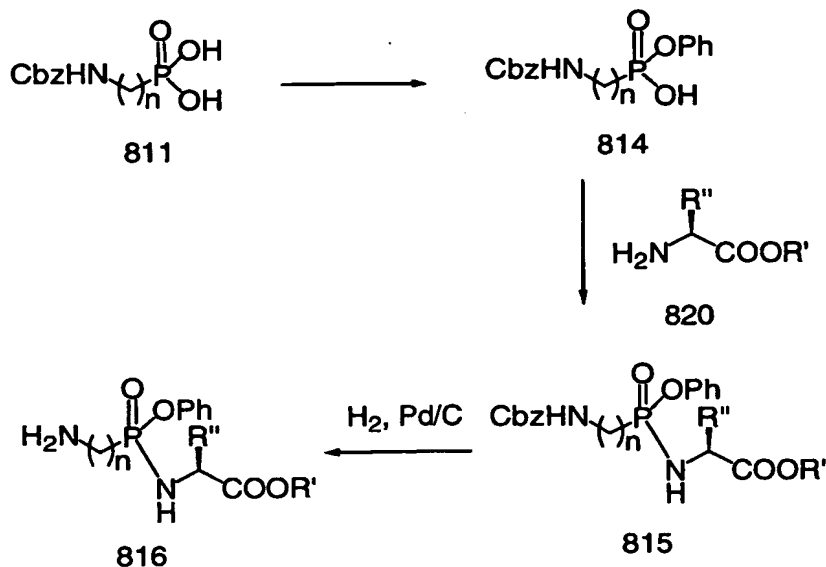
5

811 → **814**

820

816 ← **815**

Following the similar procedures, replacement of amino acid esters 820 with lactates 821 (Scheme 1003) provides mono-phosphonic lactates 823. Lactates 823 are useful intermediates to form the phosphonate compounds of the invention.

5   Scheme 1003

814   **821**   **822**   **823**

10   Scheme 1004

19   **20**

22 ← **21**
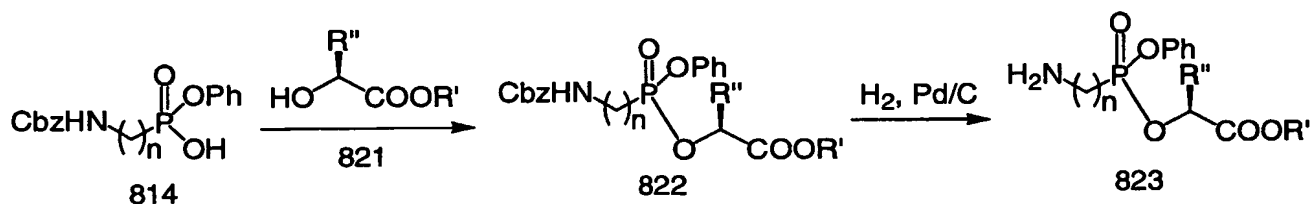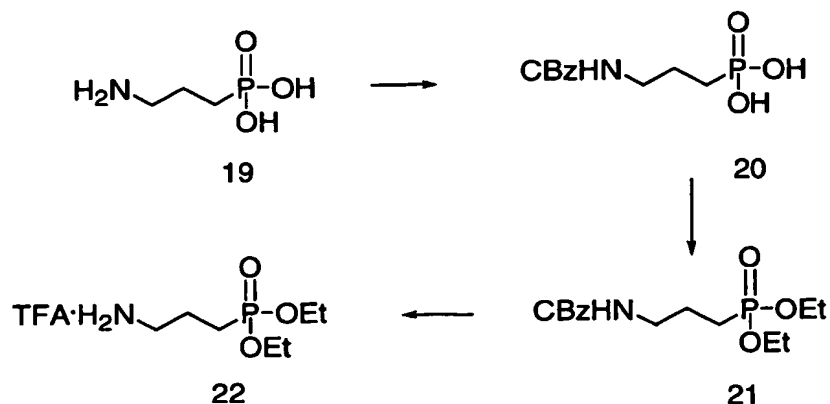
Scheme 1005

Example 1

To a solution of 2-aminoethylphosphonic acid (1.26 g, 10.1 mmol) in 2N NaOH (10.1

5   mL, 20.2 mmol) was added benzyl chloroformate (1.7 mL, 12.1 mmol). After the reaction

mixture was stirred for 2 d at room temperature, the mixture was partitioned between Et_2O

and water. The aqueous phase was acidified with 6N HCl until pH = 2. The resulting

colorless solid was dissolved in MeOH (75 mL) and treated with Dowex 50WX8-200 (7 g).

After the mixture was stirred for 30 minutes, it was filtered and evaporated under reduced

10 pressure to give carbamate **28** (2.37 g, 91%) as a colorless solid (Scheme 1005).

To a solution of carbamate **28** (2.35 g, 9.1 mmol) in pyridine (40 mL) was added

phenol (8.53 g, 90.6 mmol) and 1,3-dicyclohexylcarbodiimide (7.47 g, 36.2 mmol). After the

reaction mixture was warmed to 70°C and stirred for 5 h, the mixture was diluted with

CH_3CN and filtered. The filtrate was concentrated under reduced pressure and diluted with

15 EtOAc. The organic phase was washed with sat. NH_4Cl, sat. $NaHCO_3$, and brine, then dried

over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was

chromatographed on silica gel twice (eluting 40-60% EtOAc/hexane) to give phosphonate **29**

(2.13 g, 57%) as a colorless solid.

To a solution of phosphonate **29** (262 mg, 0.637 mmol) in iPrOH (5 mL) was added

20 TFA (0.05 mL, 0.637 mmol) and 10% Pd/C (26 mg). After the reaction mixture was stirred

under H_2 atmosphere (balloon) for 1 h, the mixture was filtered through Celite. The filtrate

was evaporated under reduced pressure to give amine **30** (249 mg, 100%) as a colorless oil

(Scheme 1005).

Scheme Section A

Exemplary methods of preparing the compounds of the invention are shown in **Schemes 1-7** below. A detailed description of the methods is found in the Experimental section below.

5

Scheme 1

Scheme 2

Scheme 3

13

14

15

Scheme 4

11   ⟶

16a-f

Scheme 5

Scheme 6

P = *tert*-butyldimethylsilyl

Scheme 7

14

29

30
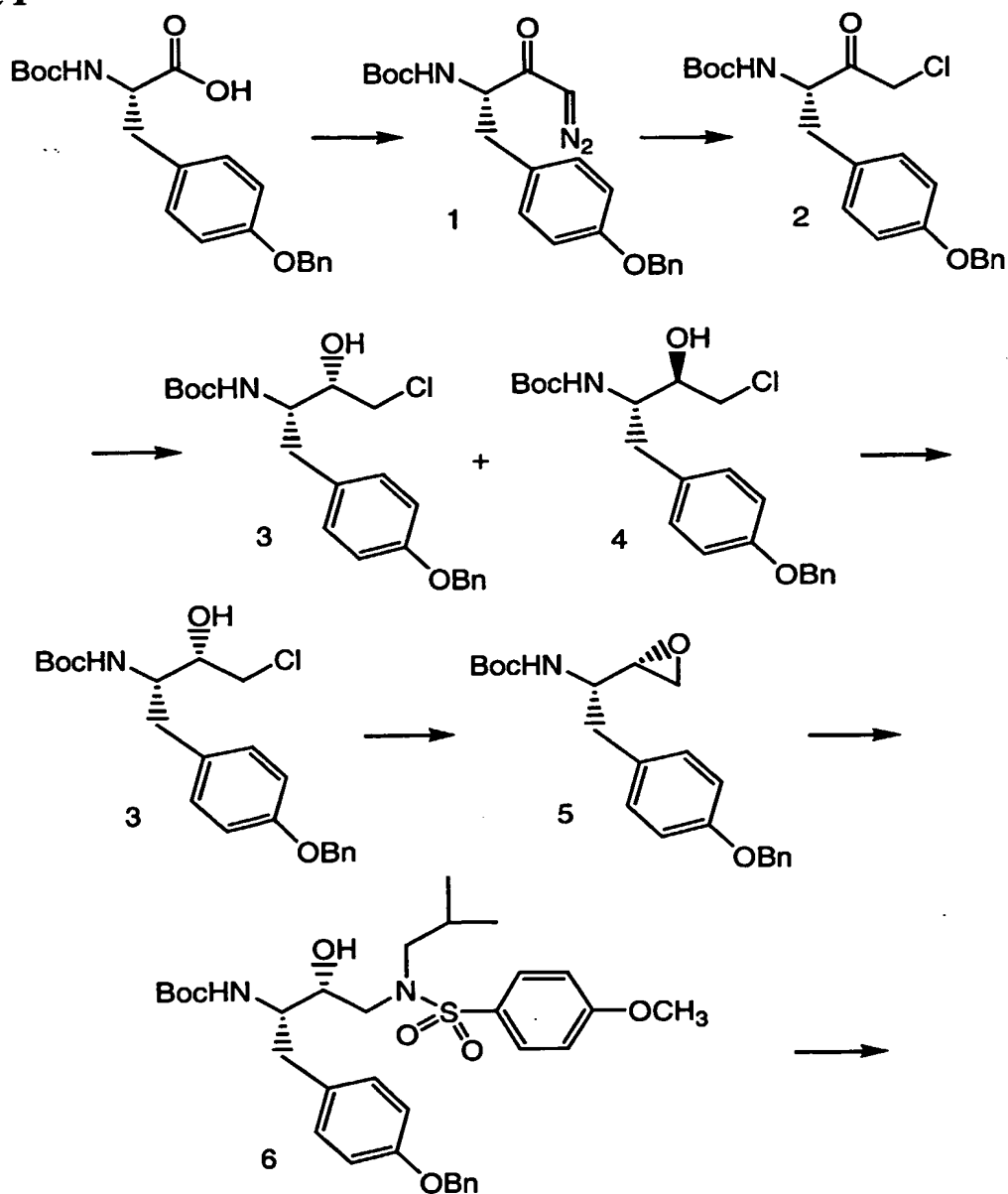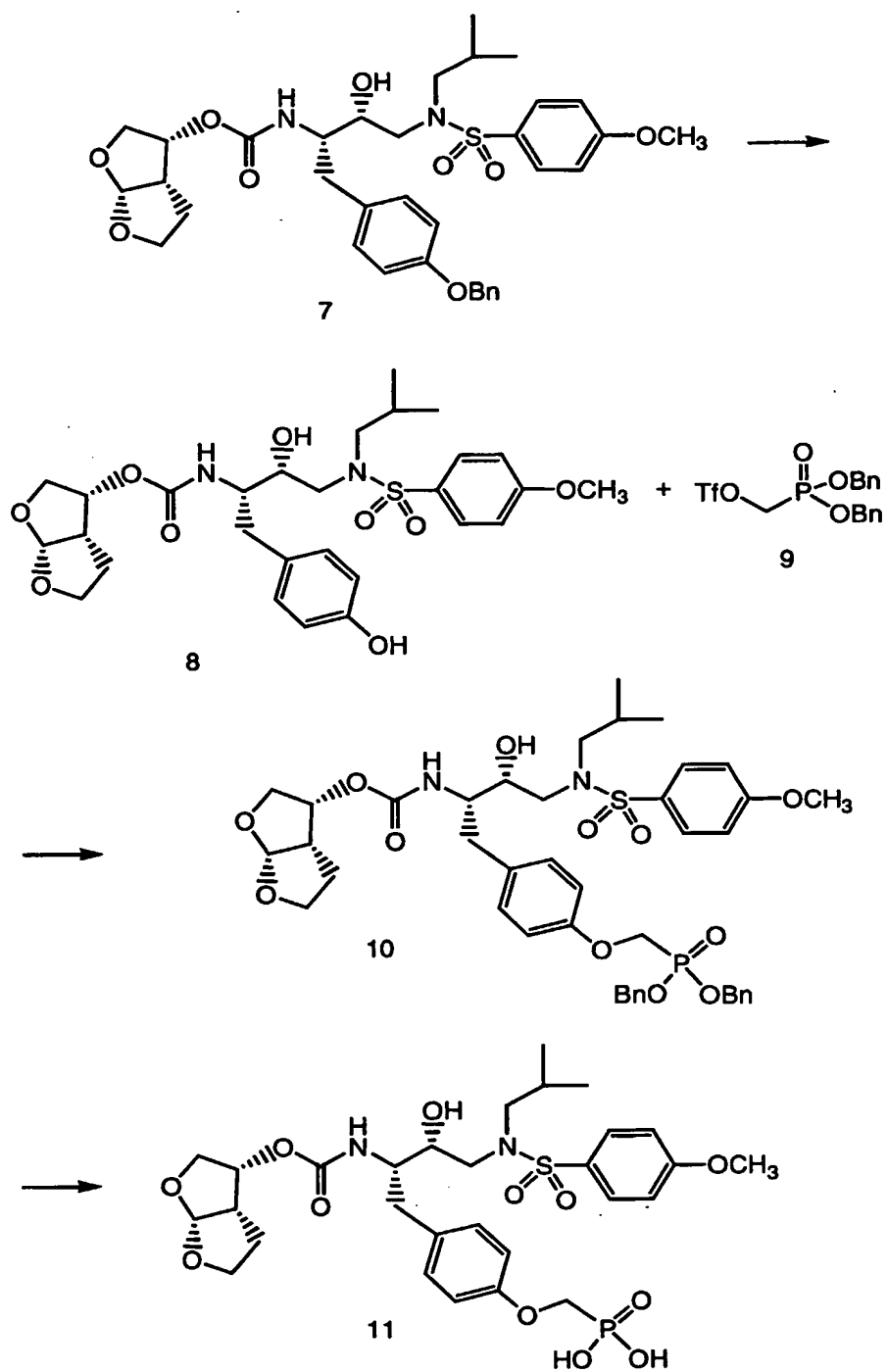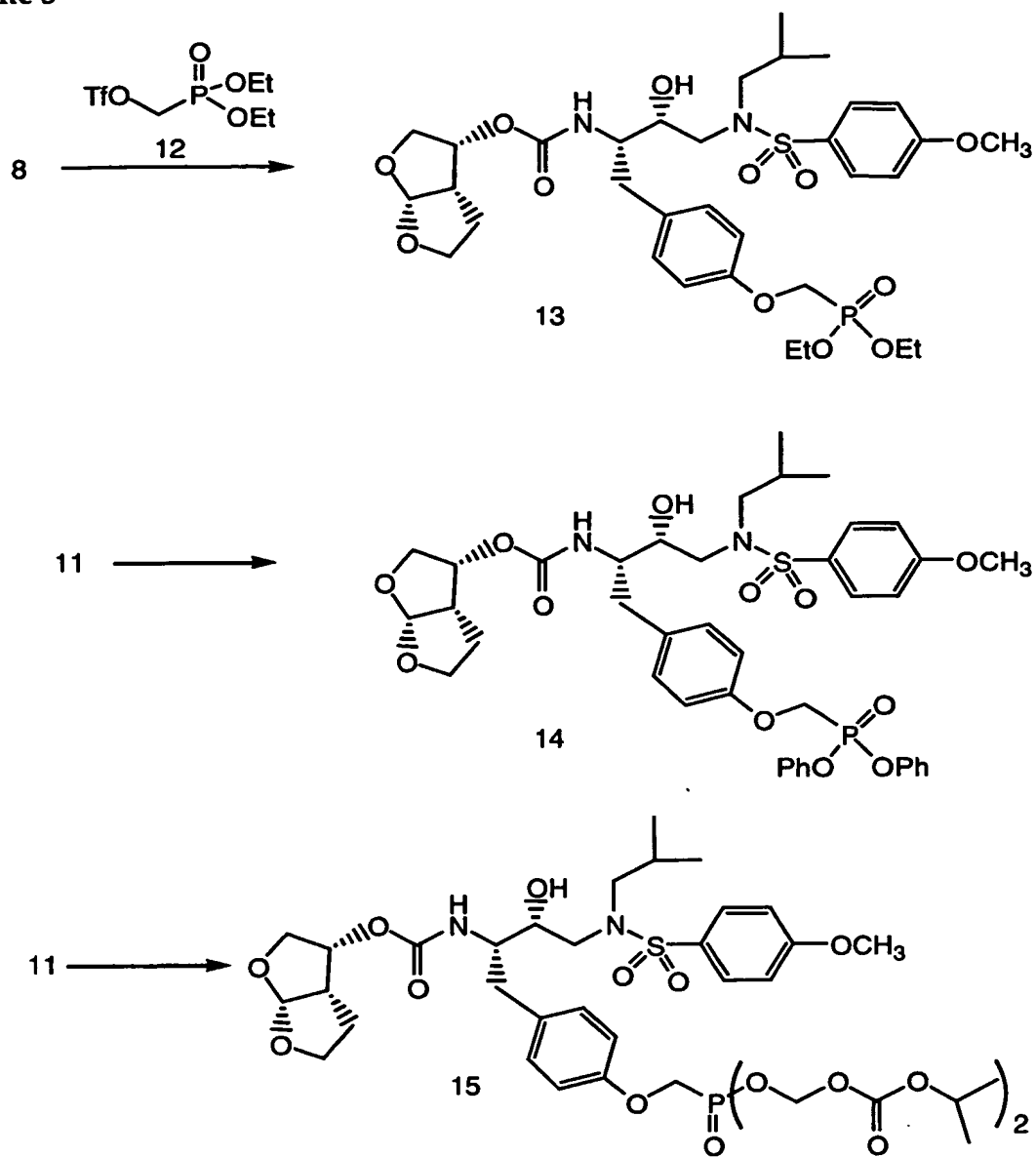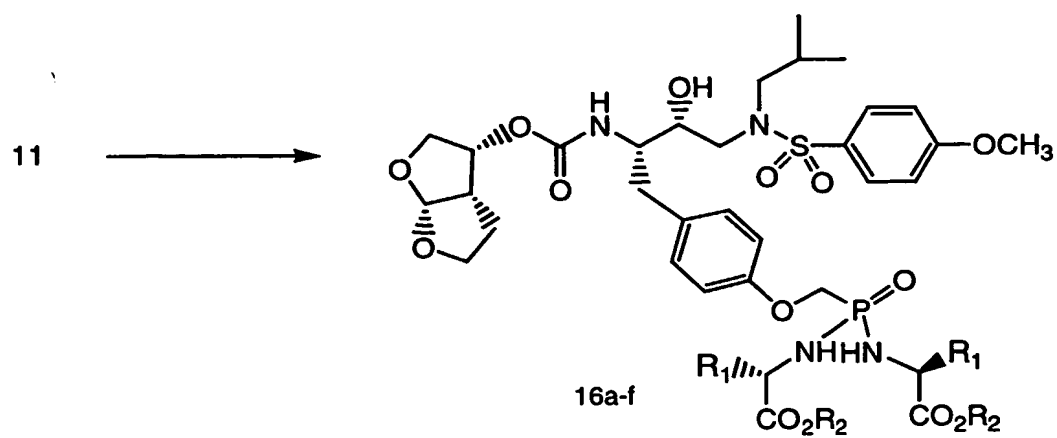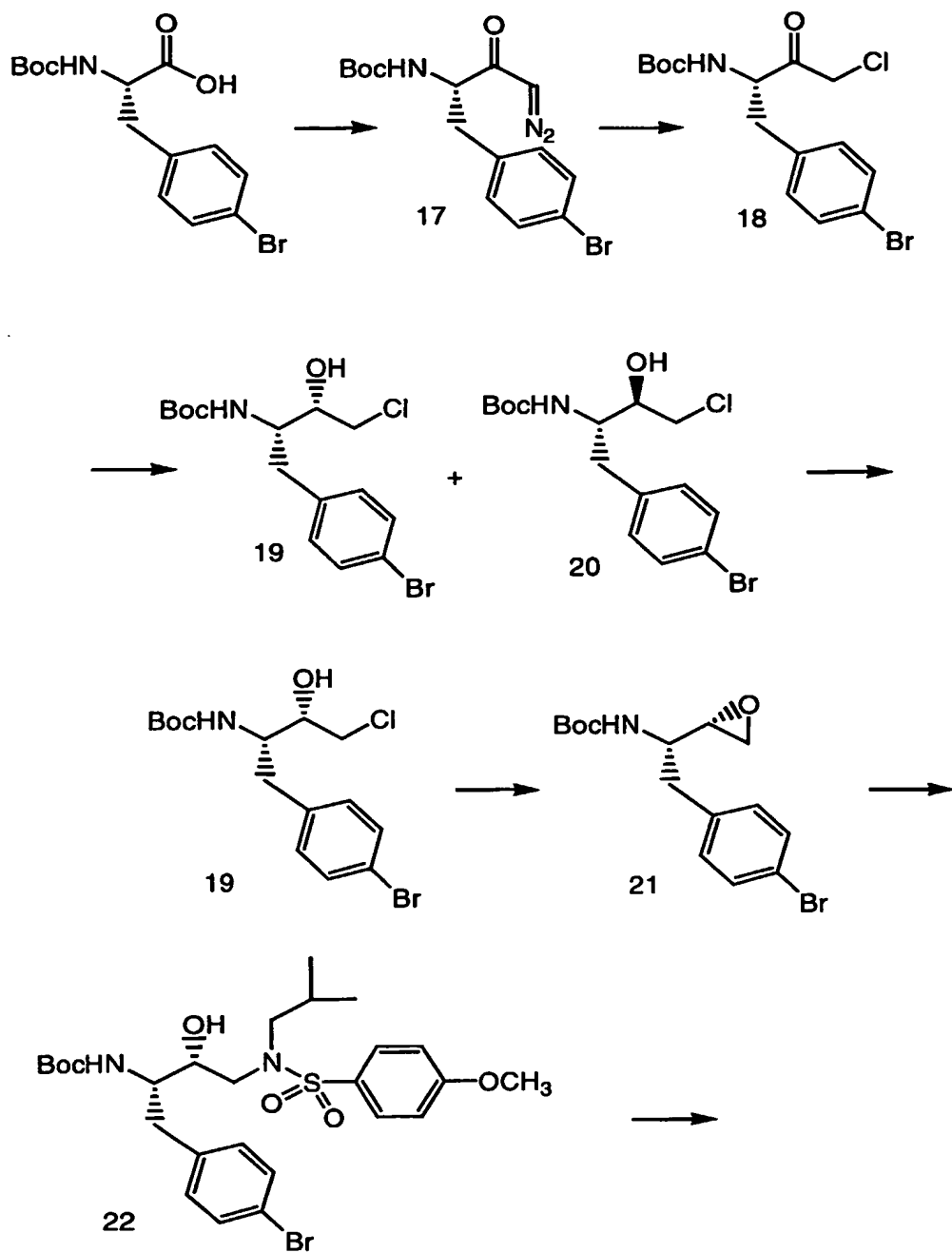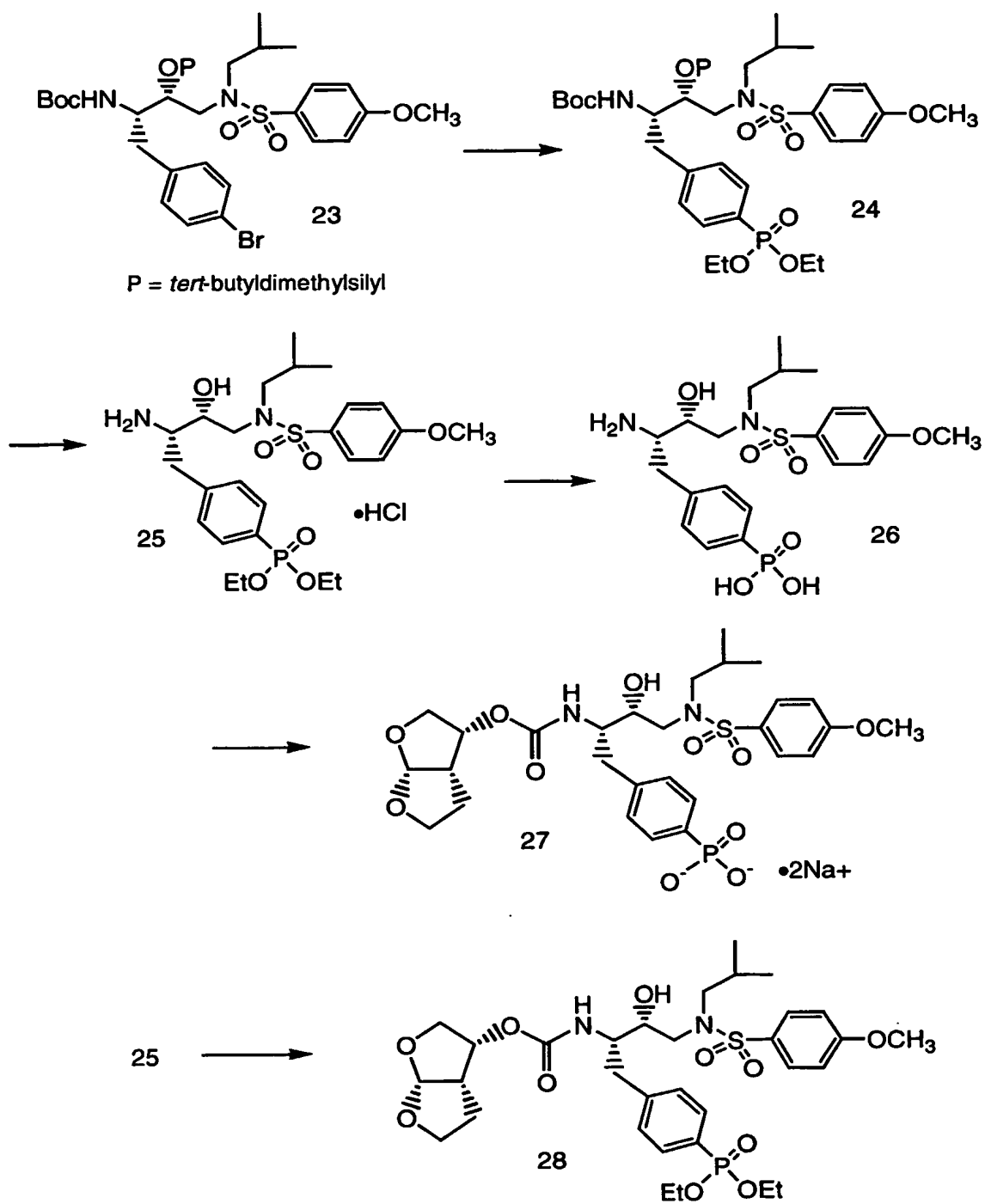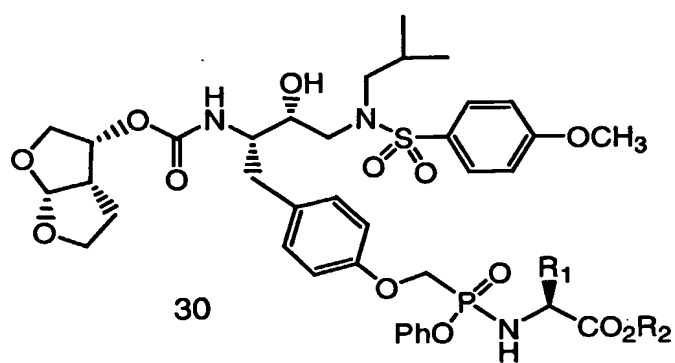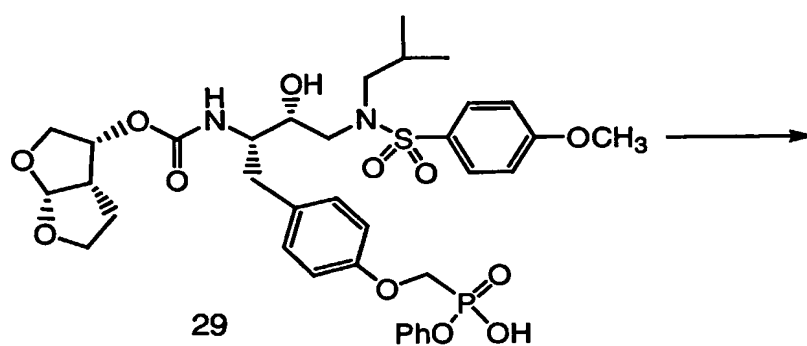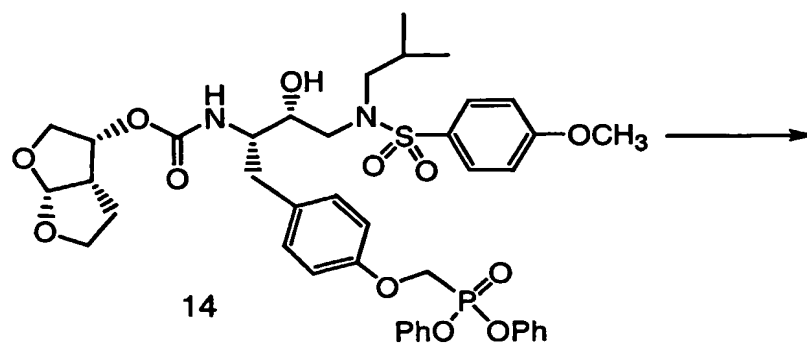
Scheme Section B

Alternative exemplary methods of preparing the compounds of the invention are shown in **Schemes 101-113** below.

5   **Scheme 101**
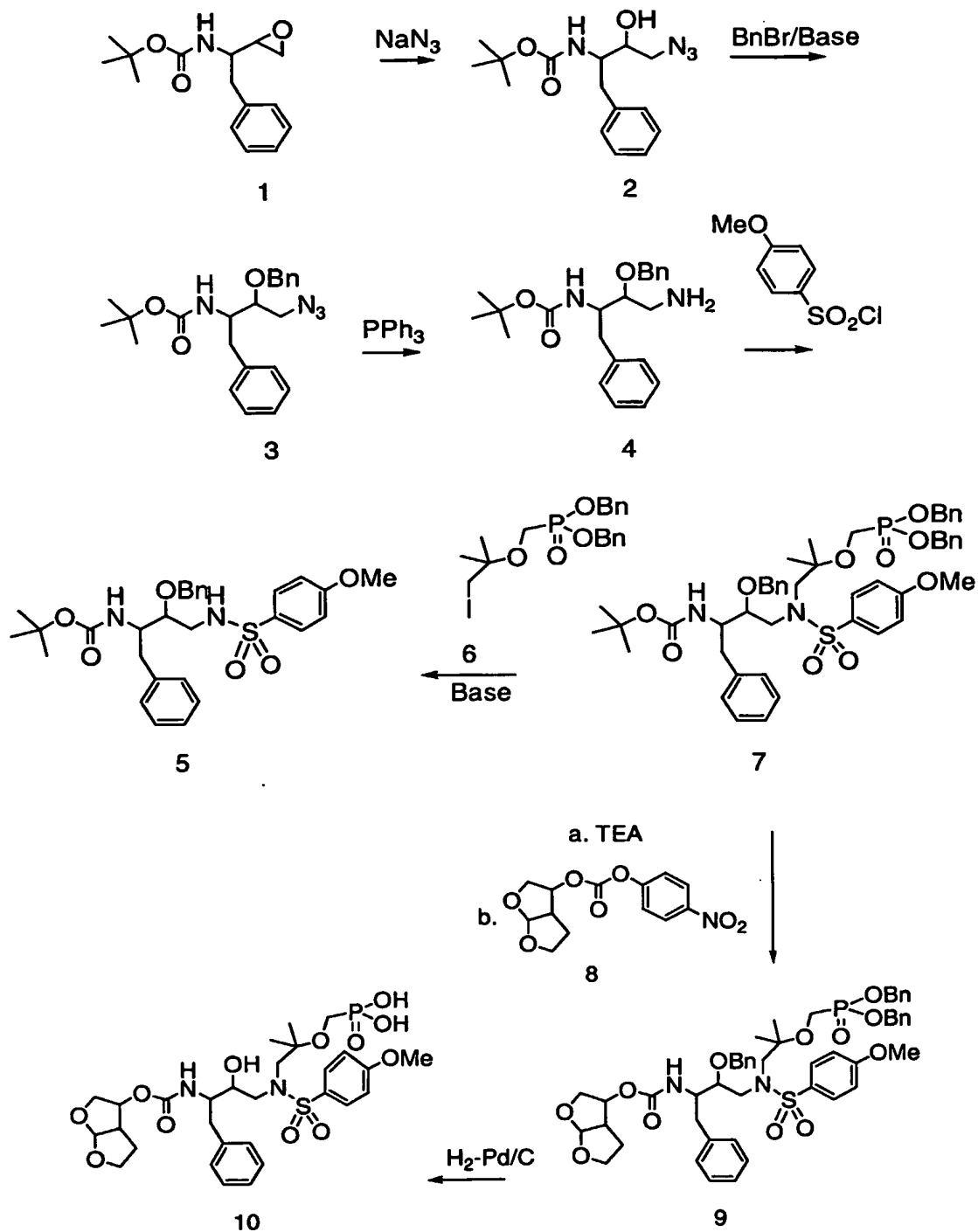
10

Treatment of commercially available epoxide 1 with sodum azide (Bioorg. & Med. Chem.

Lett., 5, 459, 1995) furnishes the azide intermediate 2. The free hydroxyl is converted to

benzyl ether 3 by treating it with benzyl bromide in the presence of base such as potassium

5   carbonate. Compound 4 is achieved by the reduction of the azide group with triphenyl

phosphine, as described in the publication Bioorg. & Med. Chem. Lett., 7, 1847, 1997.

Conversion of the amino group to its sulfonamide derivative 5 is achieved by treating the

amine with stoichiometric amounts of sulfonyl chloride. Regioselective alkylation is

performed (as shown in the article J. Med. Chem., 40, 2525, 1997) on the sulfonamide

10   nitrogen using the iodide 6 (J. Med. Chem., 35, 2958, 1992) to get the compound 7. Upon

TFA catalyzed deprotection of BOC group followed by the reaction with bisfuranyl carbonate

8 (for a similar coupling see, J. Med. Chem., 39, 3278, 1996) furnishes the compound 9.

Final deprotection of the protecting groups by catalytic hydrogenolysis result the compound

10.

Scheme 102
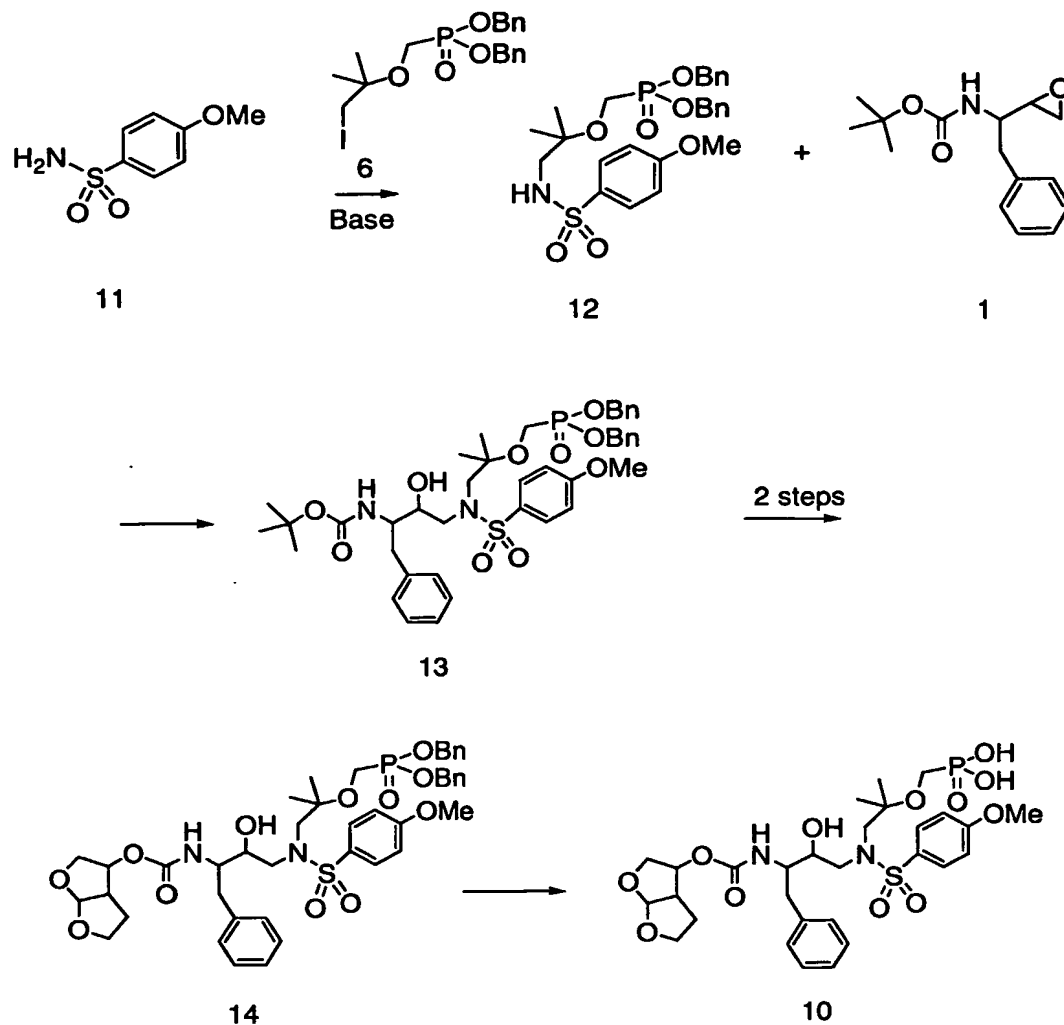
The sulfonamide 11 is readily alkylated with the iodide 6 (J. Med. Chem., 35, 2958, 1992) to get the intermediate 12. Regioselective epoxide opening (JP -9124630) of the epoxide 1 with 12 furnishes the intermediate 13. Deprotection of the BOC group followed by the treatment of bisfuranyl carbonate 8 yields the intermediate 14 which is subjected to hydrogenation to furnish the compound 10.

Scheme 103

1   15

16   13
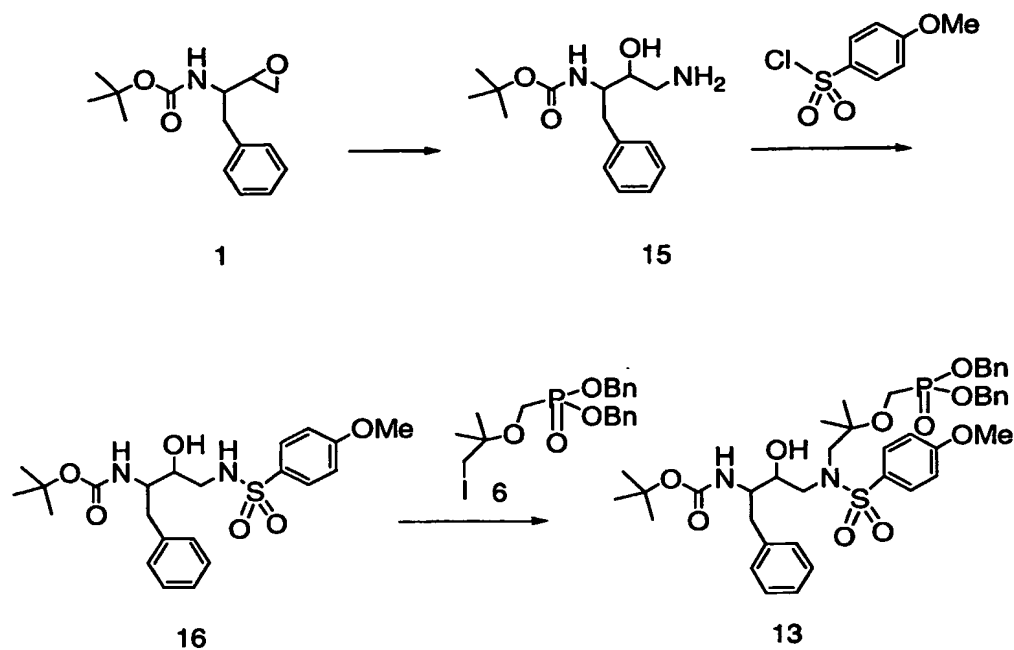
5   The epoxide 1 is converted to the aminohydroxyl derivative 15 using the known procedure (J.
     Med. Chem., 37, 1758, 1994). Sulfonylation of 15 using benzene sulfonylchloride affords
     the compound 16. Installation of the side chain to get the intermediate 13 is achieved by
     alkylation of sulfonamide nitrogen with iodide 6. The intermediate 13 is converted to the
     compound 10 using the same sequence as shown in scheme 102.

Scheme 104
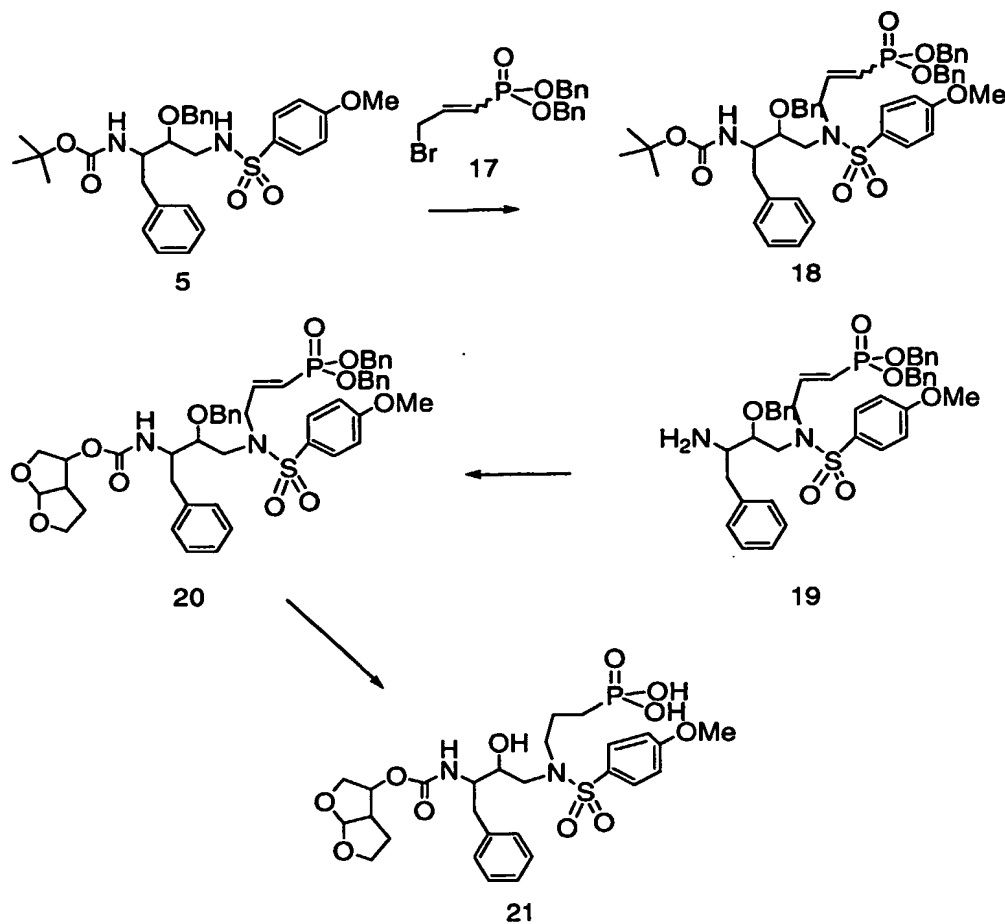
5

Sulfonamide 5 is alkylated under basic conditions using the allyl bromide 17 (Chem. Pharm. Bull., 30, 111, 1982) to get the intermediate 18. Similar transformation is reported in literature (J. Med. Chem., 40, 2525, 1997). Hydrolysis of BOC group with TFA and acylation of the resulting amine 19 with bisfuranyl carbonate 8 yields the compound 20.

10   Hydrogenation using Pd/C catalysis under H_2 atmosphere affords the phosphonic acid 21.

Scheme 105
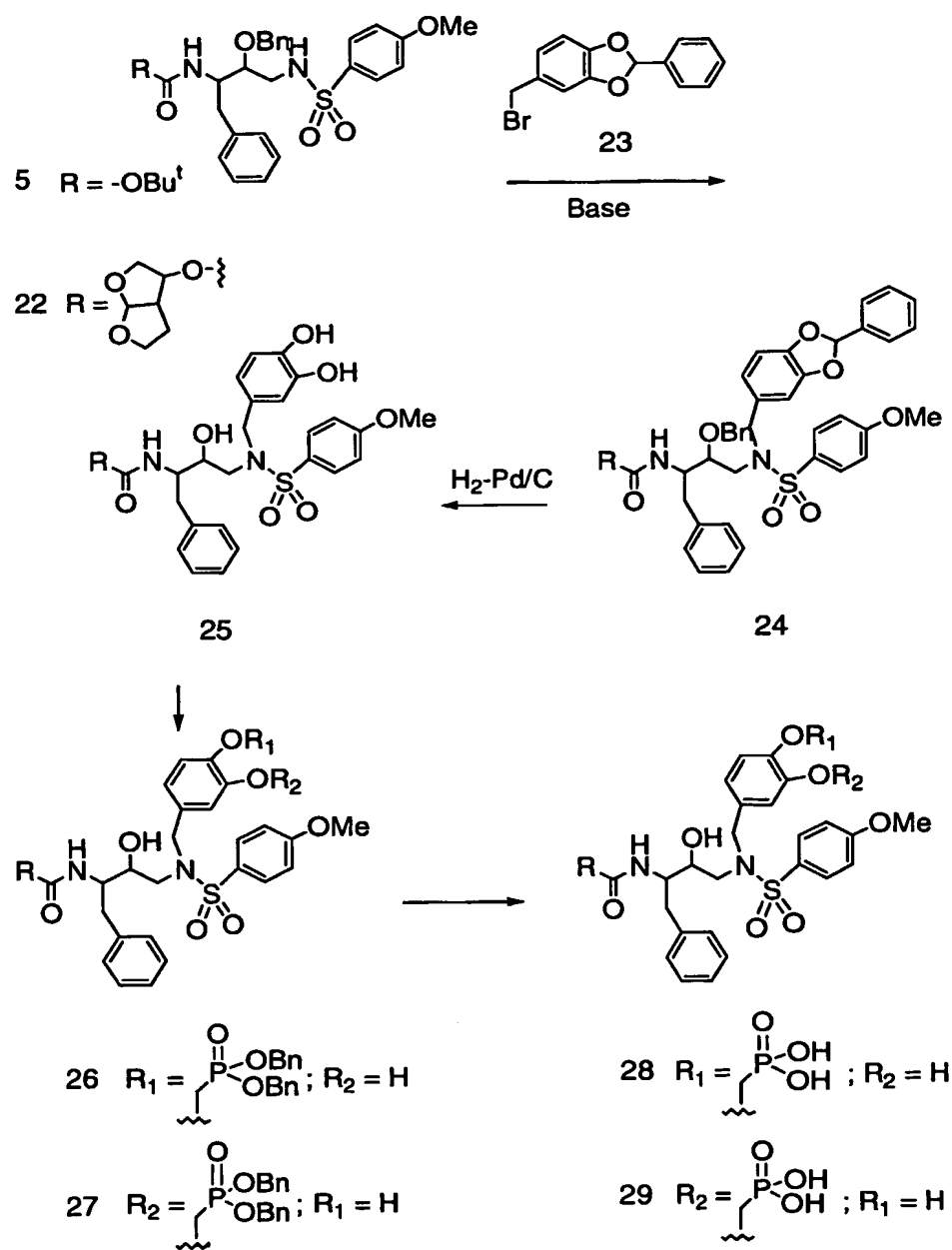
Scheme 105 (cont)
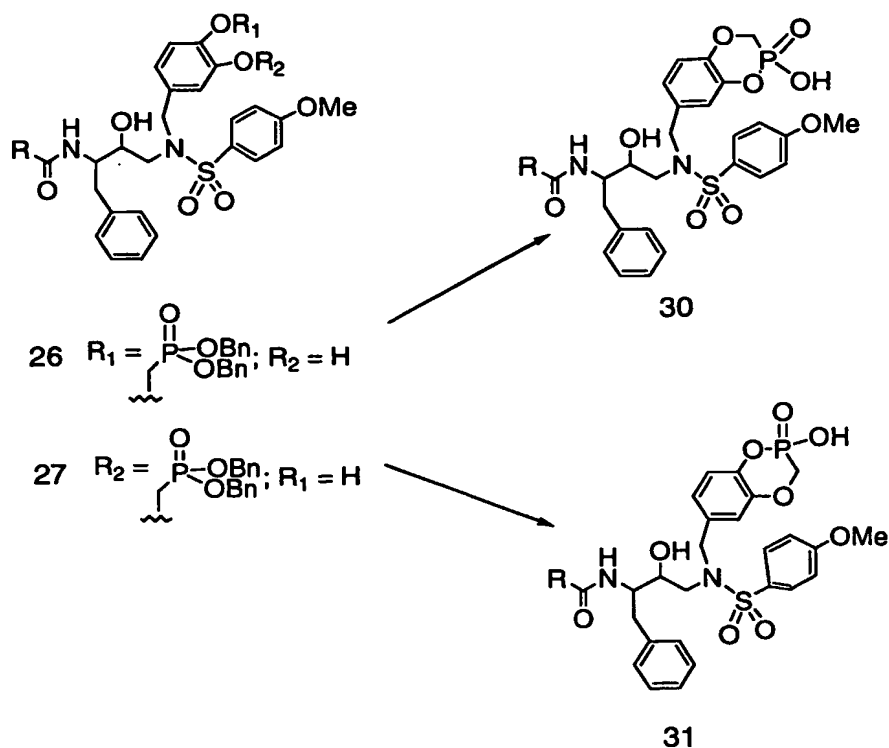
Sulfonamide 5 is converted to 22 via hydrolysis of BOC group with TFA and acylation with bisfuranyl carbonate 8. The sulfonamide 22 is alkylated with the bromide 23 (J. Med. Chem., 40, 2525, 1997) to get the compound 24, which upon hydrogenolysis gives the catechol 25. Alkylation of the phenolic groups using dibenzylhydroxymethyl phosphonate (J. Org. Chem., 53, 3457, 1988) affords regioisomeric compounds 26 and 27. These compounds 26 and 27 are hydrogenated to get the phophonic acids 28 and 29, respectively. Individual cyclic phosphonic acids 30 and 31 are obtained under basic (like NaH) conditions (US 5886179) followed by hydrogenolysis of the dibenzyl ester derivatives 26 and 27.

Scheme 106

In this route, compound 25 is obtained by conducting a reaction between the epoxide 32 and

5   the sulfonamide 33 using the conditions described in the Japanese Patent No. 9124630.
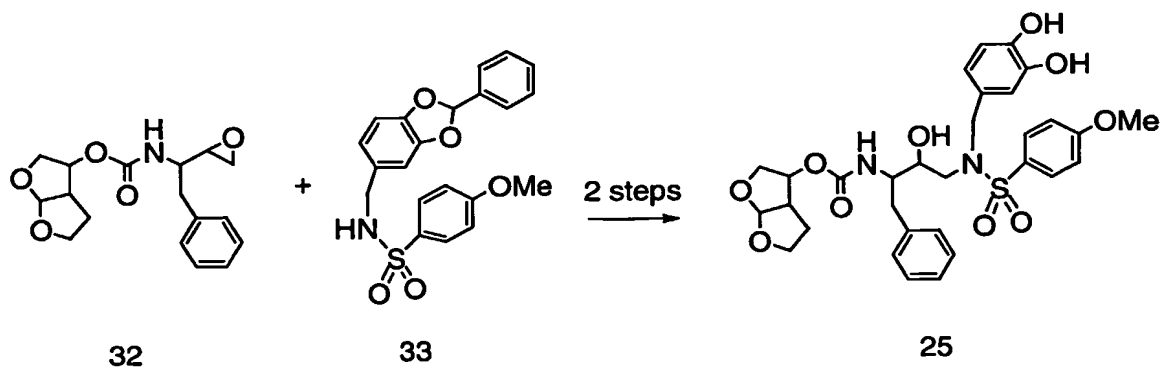
10   Epoxide 32 and sulfonamide 33 are synthesized utilizing similar methodology delineated in

the same patent.

Scheme 107
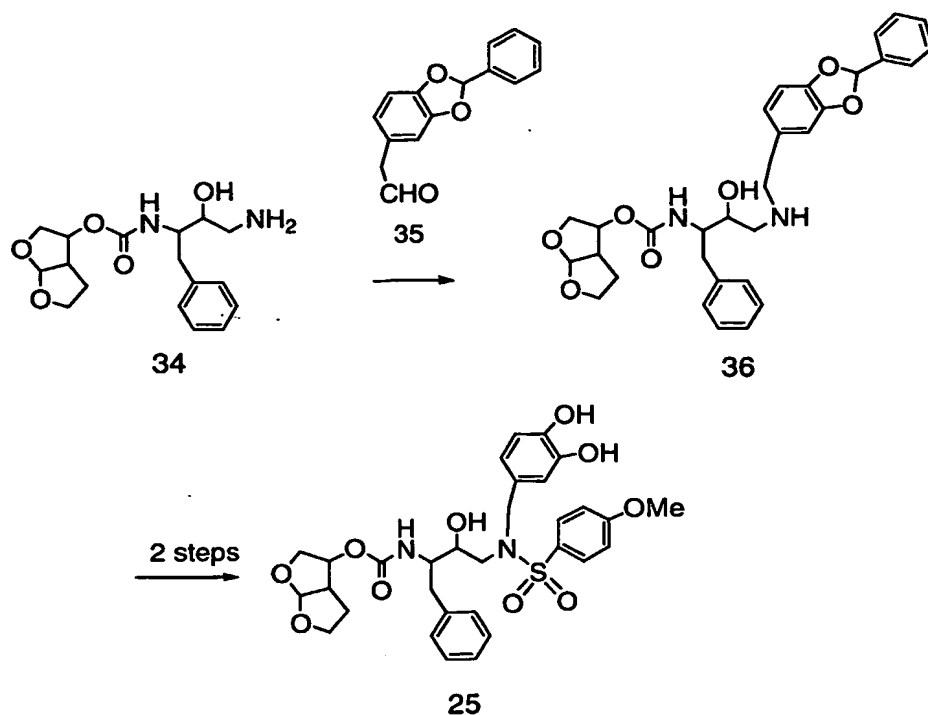
Compound 34 is obtained from 32 using similar sequence depicted in J. Med. Chem., 37, 1758, 1994. Reductive amination (for similar transformation see WO 00/47551) of compound 34 with aldehyde 35 furnishes the intermediate 36 which is converted to the compound 25 by sulfonylation followed by hydrogenation.

Scheme 108

32

37 $R_1 = \overset{O}{\underset{}{P}}\!\!\!<\!\!\!\begin{smallmatrix}OBn\\OBn\end{smallmatrix}$; $R_2 = H$

26 $R_1 = \overset{O}{\underset{}{P}}\!\!\!<\!\!\!\begin{smallmatrix}OBn\\OBn\end{smallmatrix}$; $R_2 = H$

38 $R_2 = \overset{O}{\underset{}{P}}\!\!\!<\!\!\!\begin{smallmatrix}OBn\\OBn\end{smallmatrix}$; $R_1 = H$

27 $R_2 = \overset{O}{\underset{}{P}}\!\!\!<\!\!\!\begin{smallmatrix}OBn\\OBn\end{smallmatrix}$; $R_1 = H$
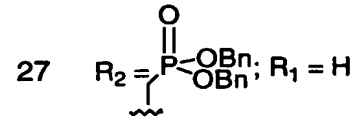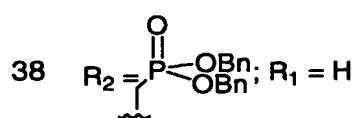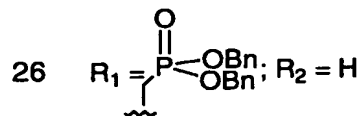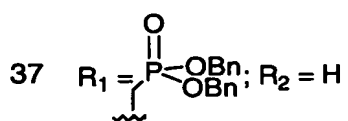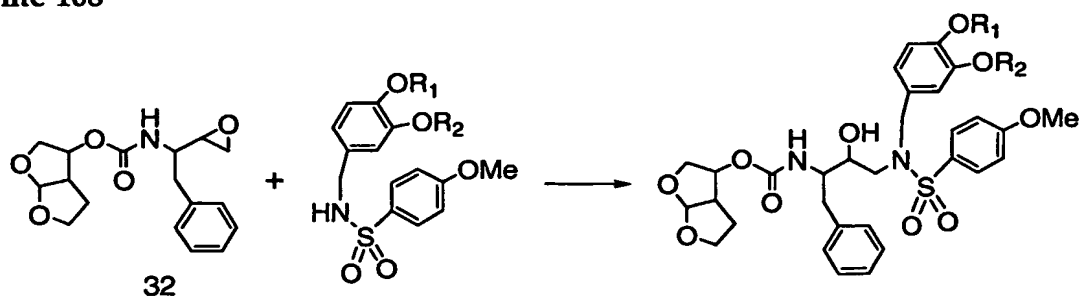
5   Treatment of epoxide 32 with sulfonamides 37 and/or 38 under conditions described in Japanese Patent No. 9124630 furnishes 26 and 27.

Scheme 109

Reductive amination of aminohydroxyl intermediate 34 with the aldehydes 39 and 40 as
described in patent WO 00/47551, furnish 41 and 42 which undergoes smooth sulfonylation
to give 26 and 27.
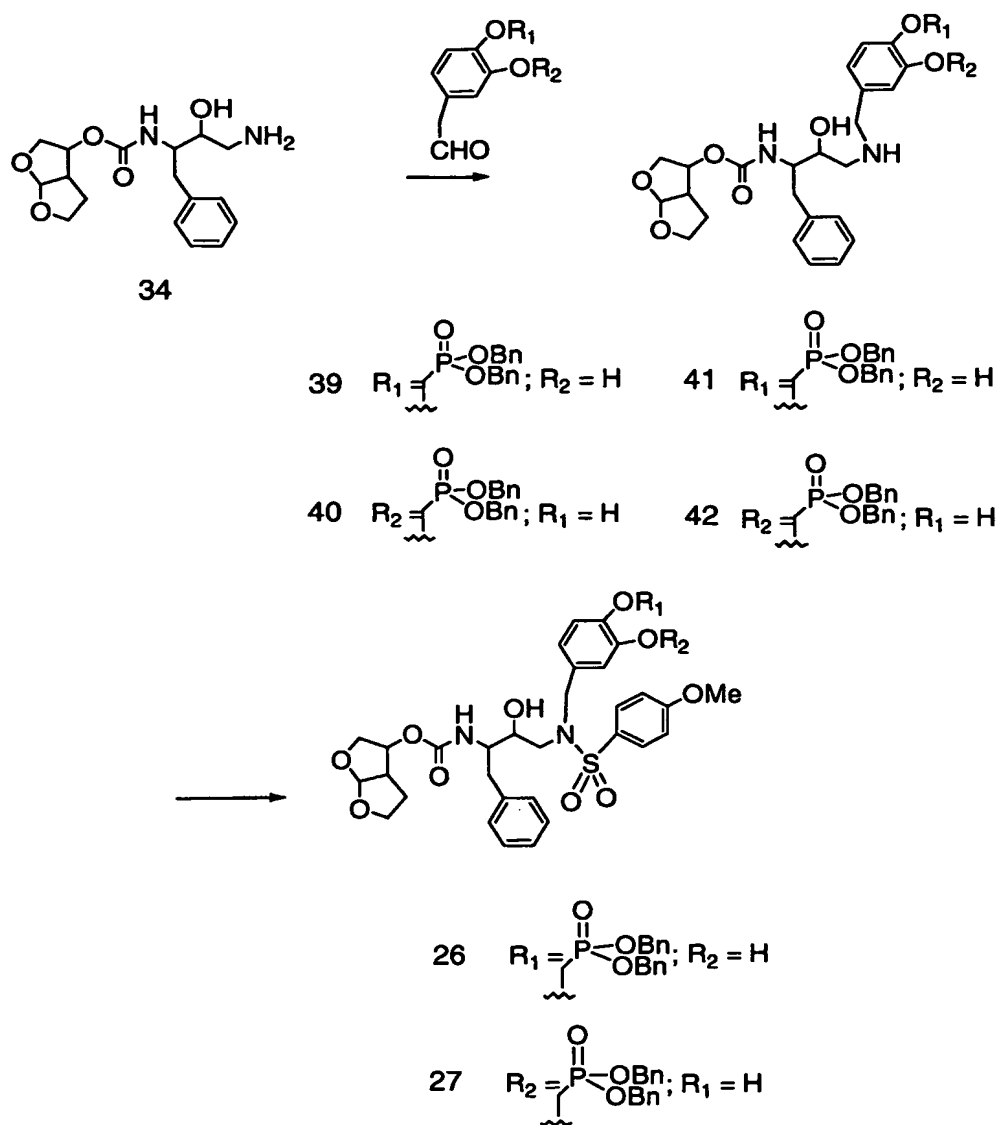
Scheme 110

In an alternate approach, where epoxide 32 is opened with benzyl amines 43 and 44 under

5   conditions described above furnishes 41 and 42, respectively. Similar transformations were

documented in the Japanese Patent No. 9124630.

32

43    $R_1 = \overset{O}{\underset{||}{P}}\langle \overset{OBn}{OBn}; R_2 = H$ 41 $R_1 = \overset{O}{\underset{||}{P}}\langle \overset{OBn}{OBn}; R_2 = H$

44    $R_2 = \overset{O}{\underset{||}{P}}\langle \overset{OBn}{OBn}; R_1 = H$ 42 $R_2 = \overset{O}{\underset{||}{P}}\langle \overset{OBn}{OBn}; R_1 = H$

Scheme 111

34

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49
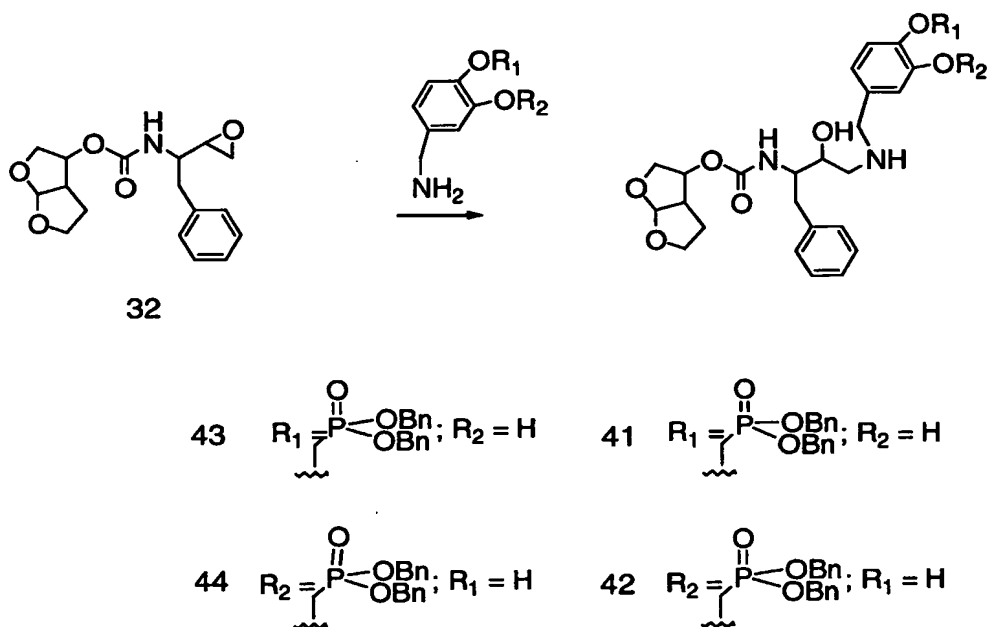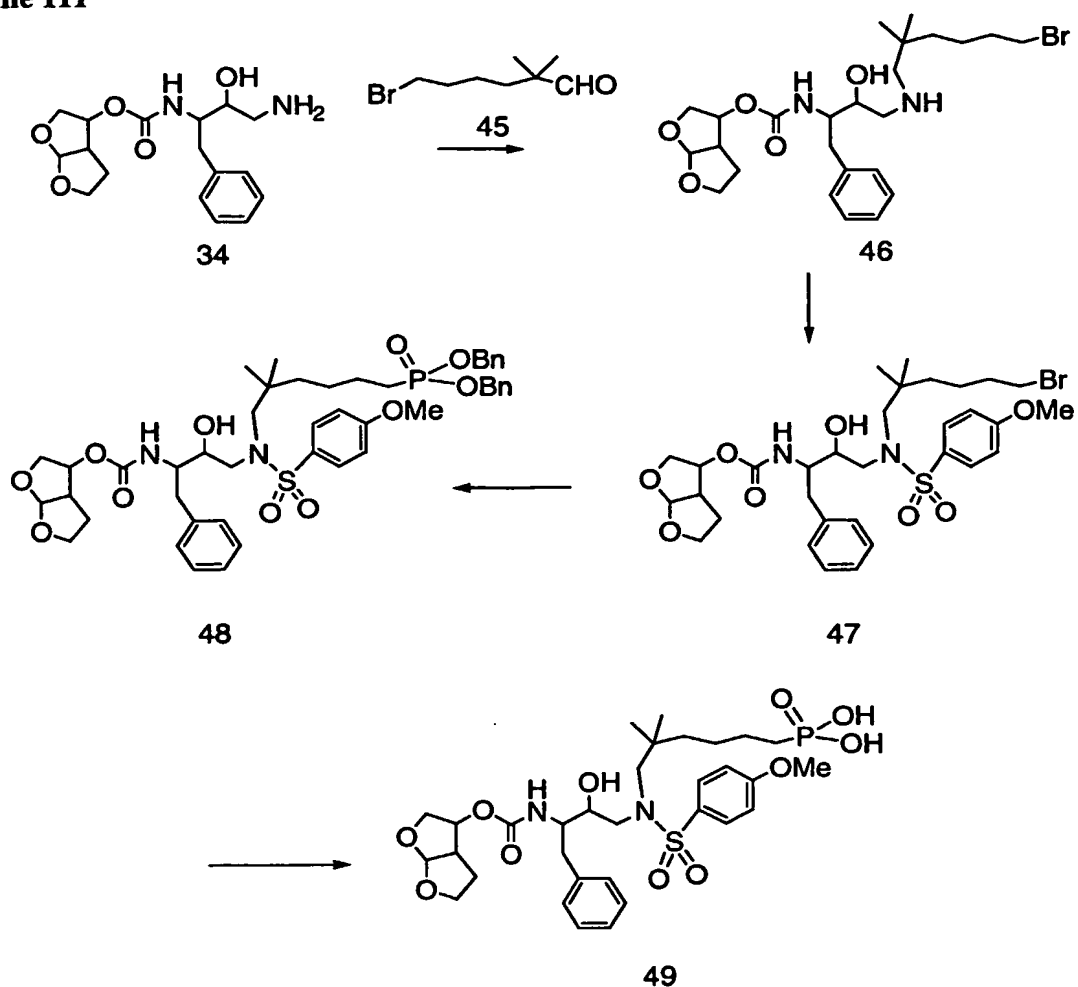
Reductive amination of the bromoaldehyde 45 (J. Organomet. Chem., FR; 122, 123, 1976) with the amine 34 gives 46 which then undergoes sulfonylation to furnish 47. The bromoderivative 47 is converted to the phosphonate 48 under Michaelis-Arbuzov reaction conditions (Bioorg. Med. Chem. Lett., 9, 3069, 1999). Final hydrogenation of 48 delivers the phosphonic acid 49.
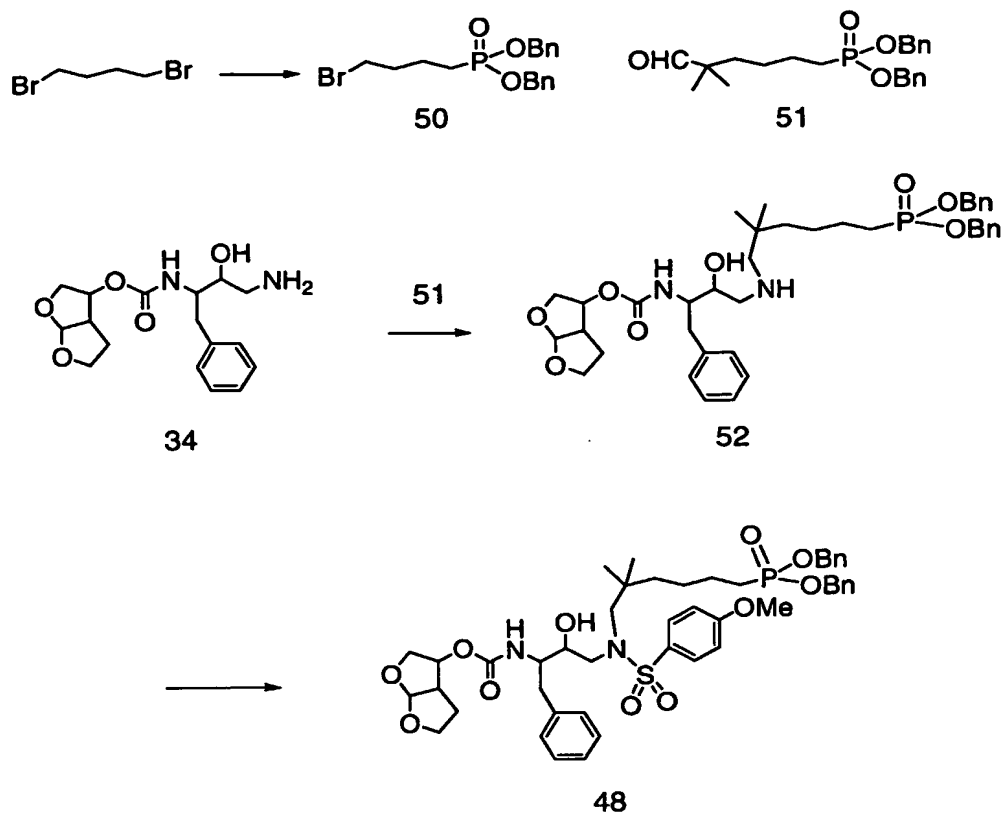
Scheme 112

The intermediate 48 is also obtained as shown in scheme 112. Reductive amination of the aldehyde 52 with the amine 34 offers the phosphonate 52 and sulfonylation of this intermediate furnishes 48.

Scheme 113
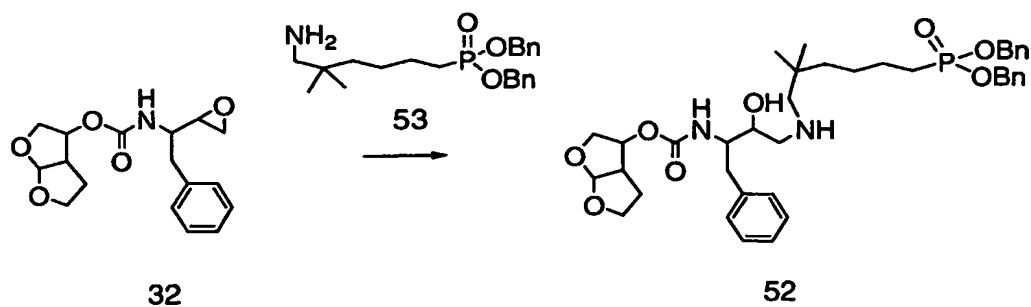
5   32   52

Alternatively, compound 52 is obtained from the epoxide 32 by a ring opening reaction with

10   the aminophosphonate 53 (Scheme 113).

Scheme Section C

Scheme 9 is described in the Examples.

5   **Scheme 9**

30

31

32

33
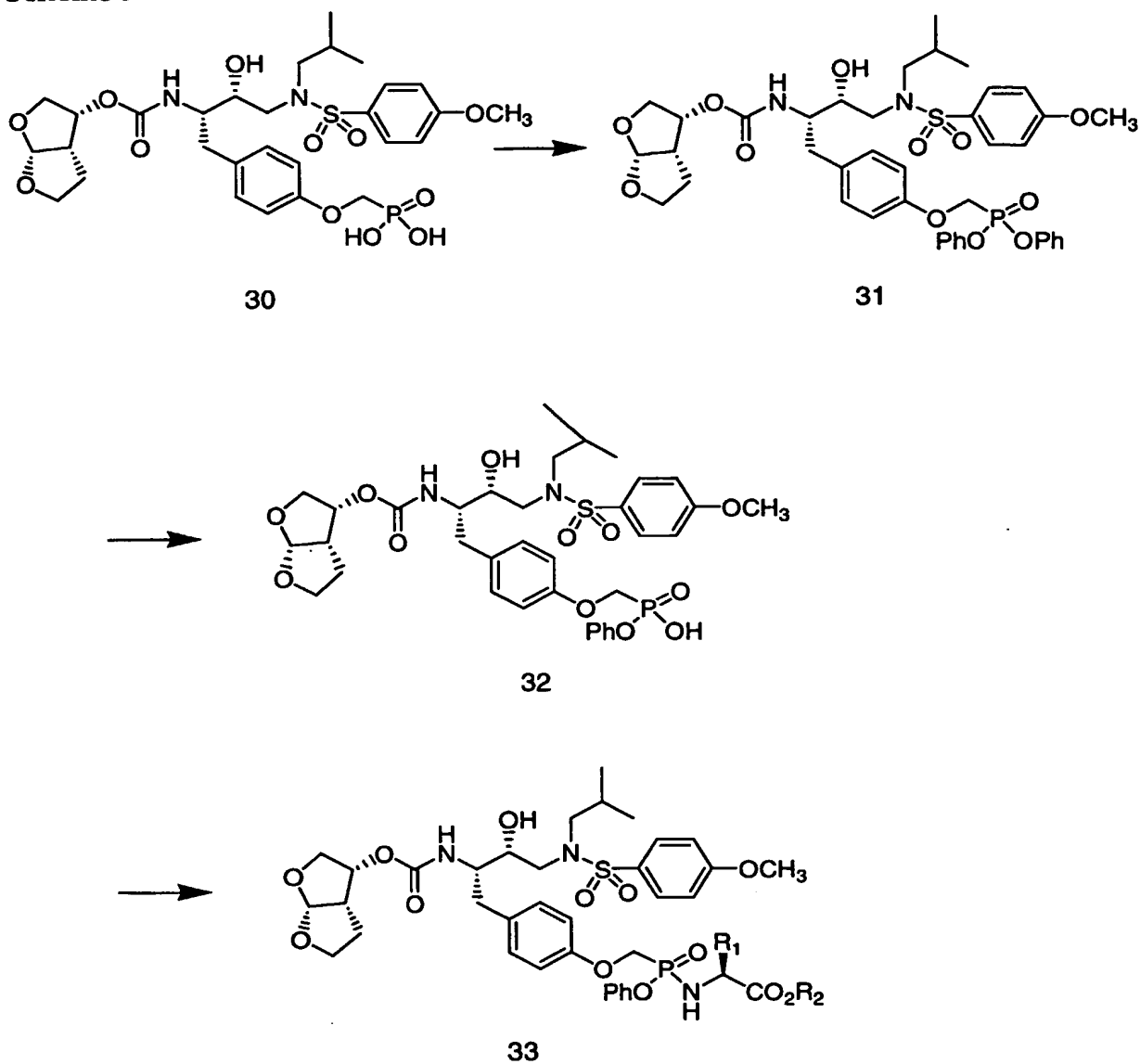
Scheme Section D

The following schemes are described in the Examples.

11

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21
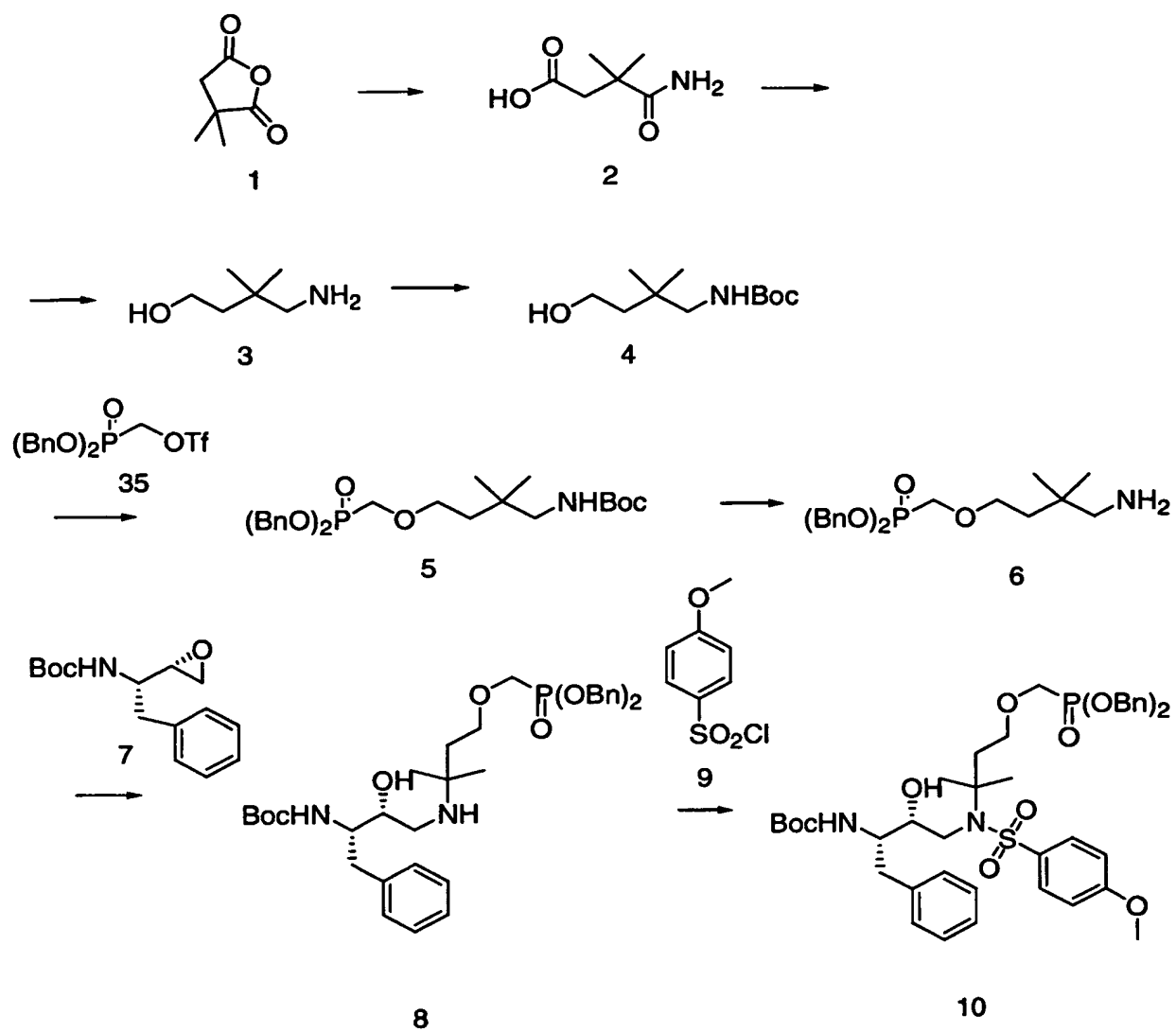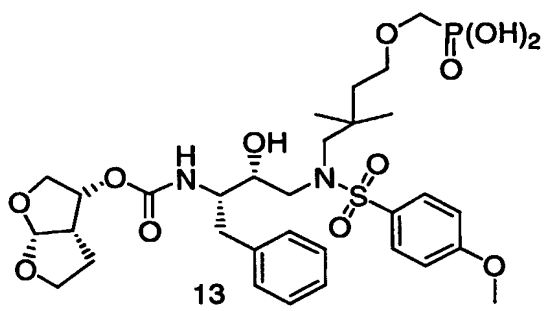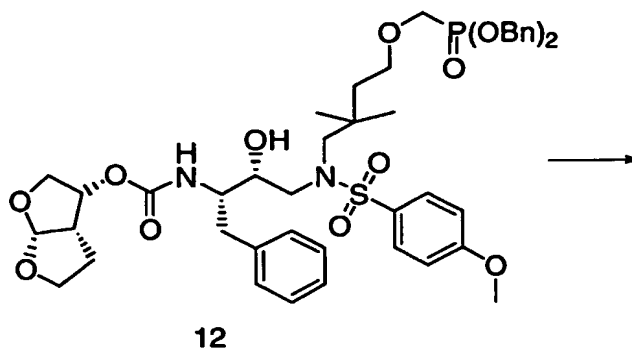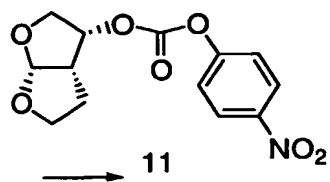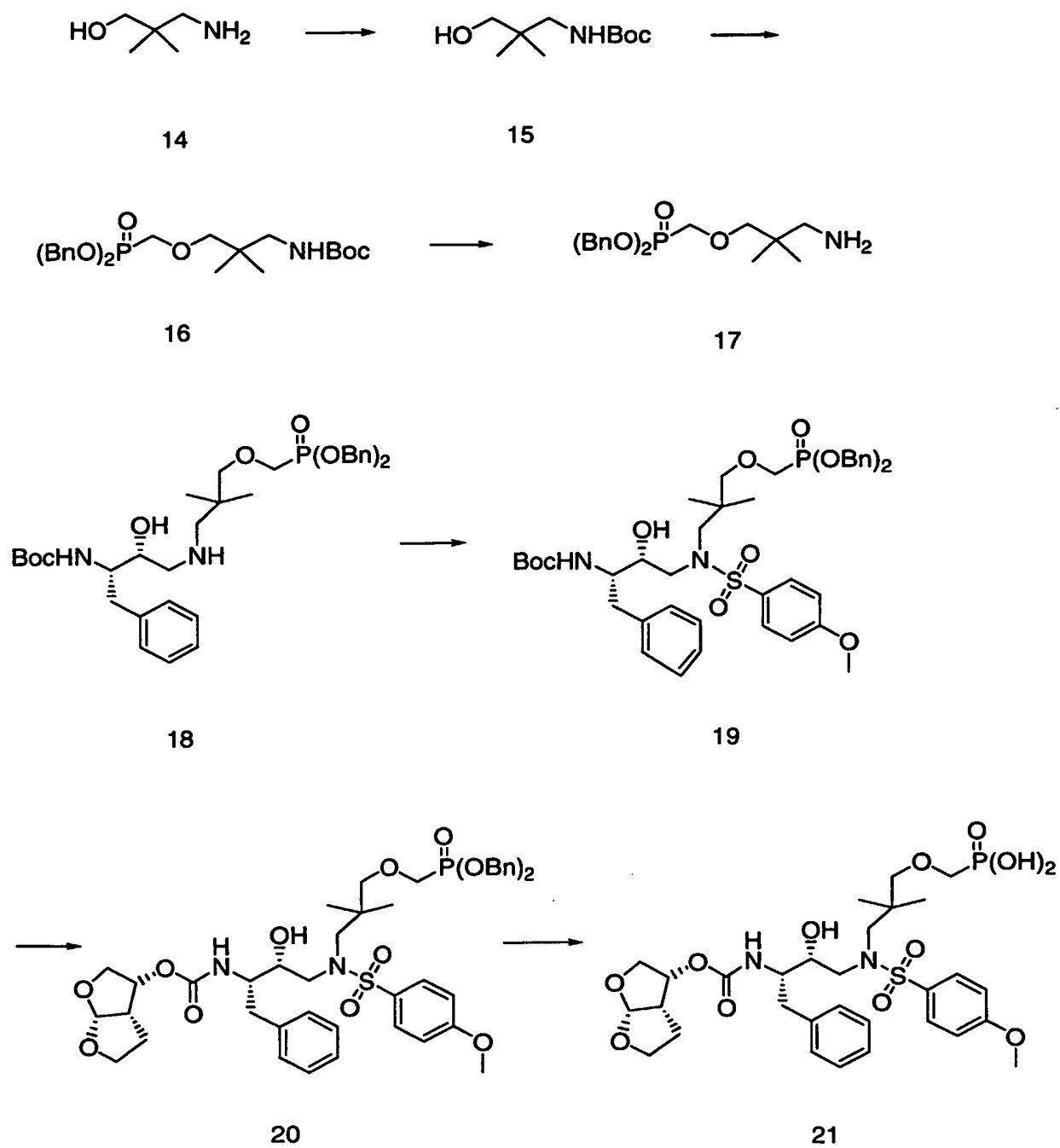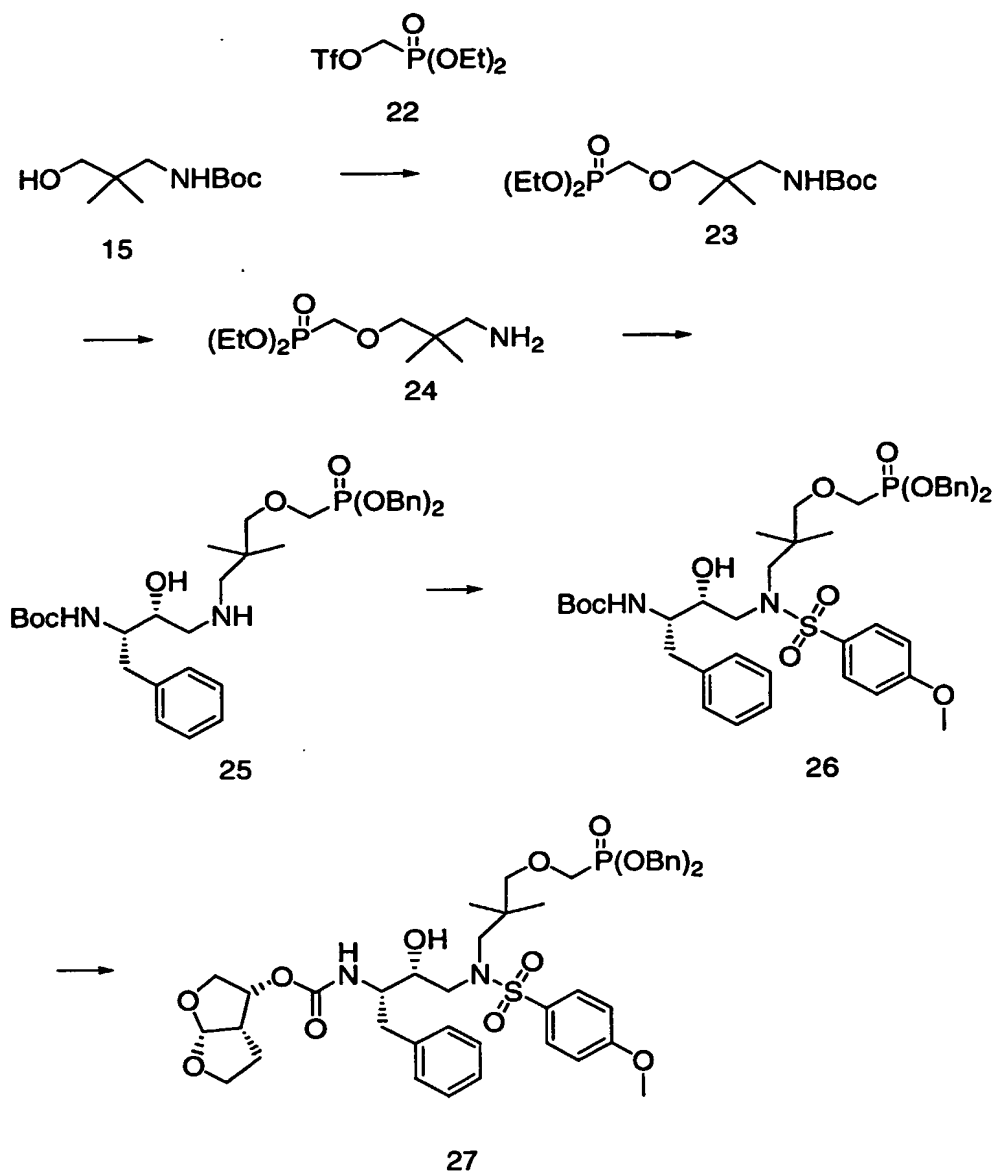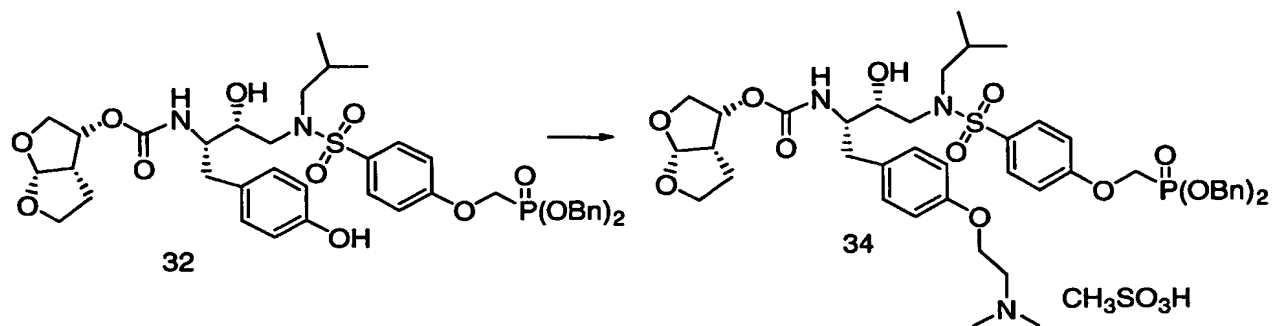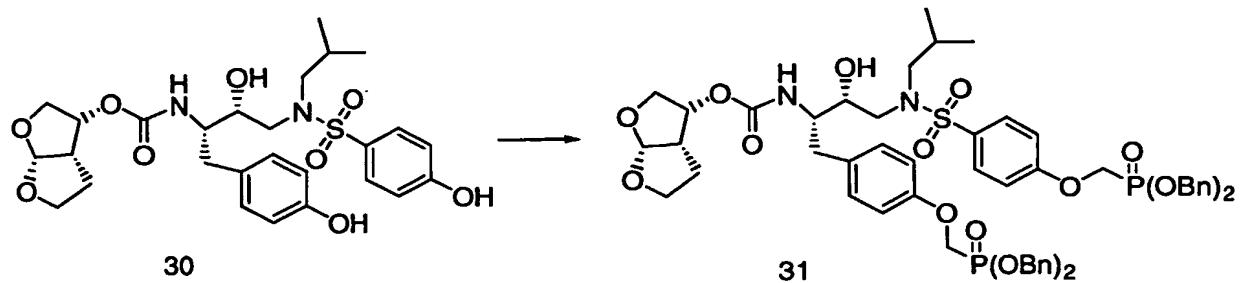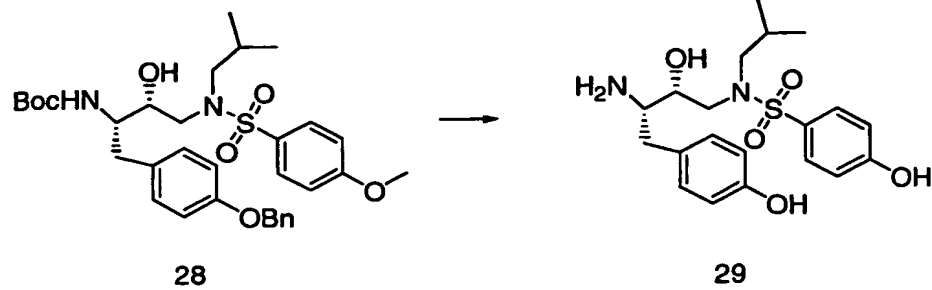
Scheme Section E

Schemes 1-3 are described in the examples.
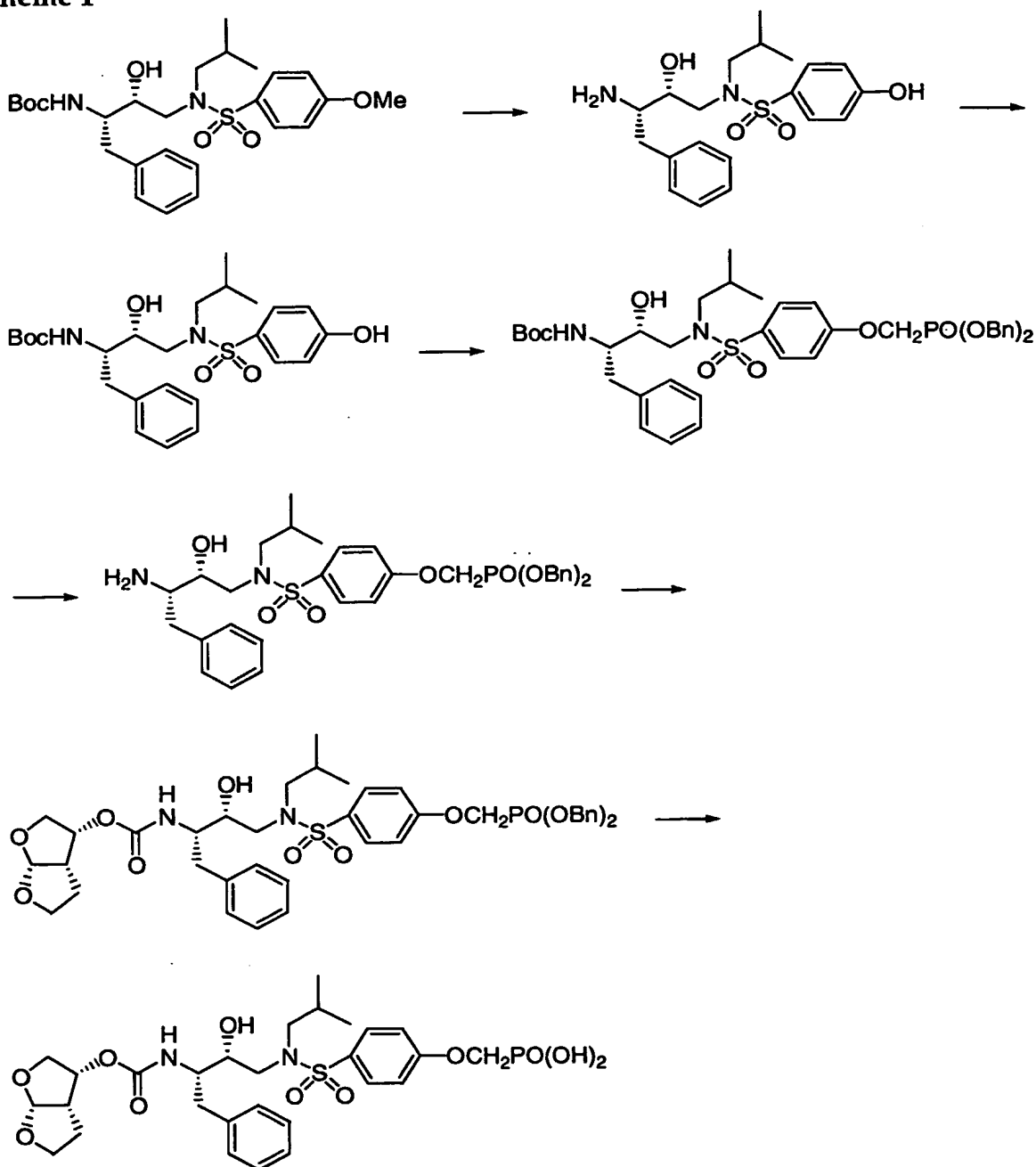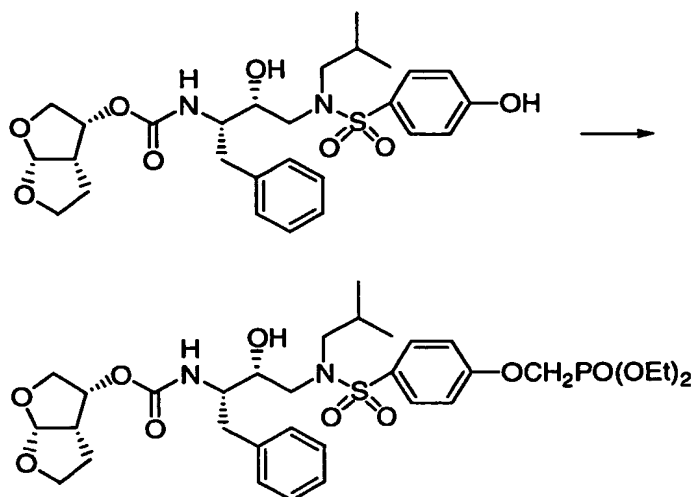
Scheme 1

Scheme 2

5

Scheme 3
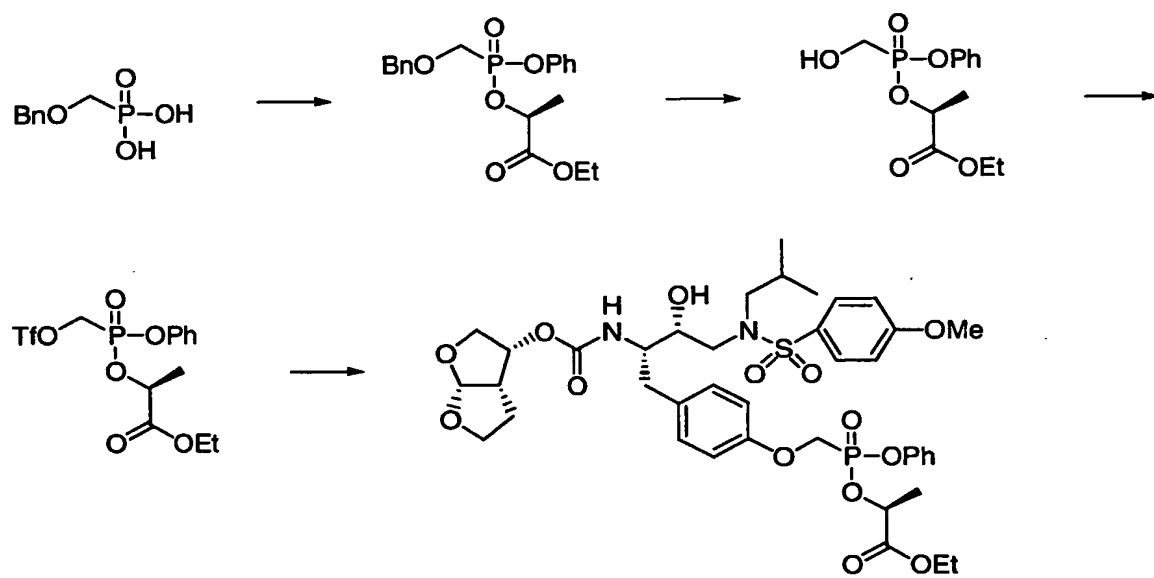
Scheme Section F

Schemes 1-5 are described in the examples.

Scheme 1

5

1 → 2 → 3

4 → 5

6

Scheme 2

Scheme 3

Scheme 4

15

16

17

18

19

5

Scheme 5

17

20

21
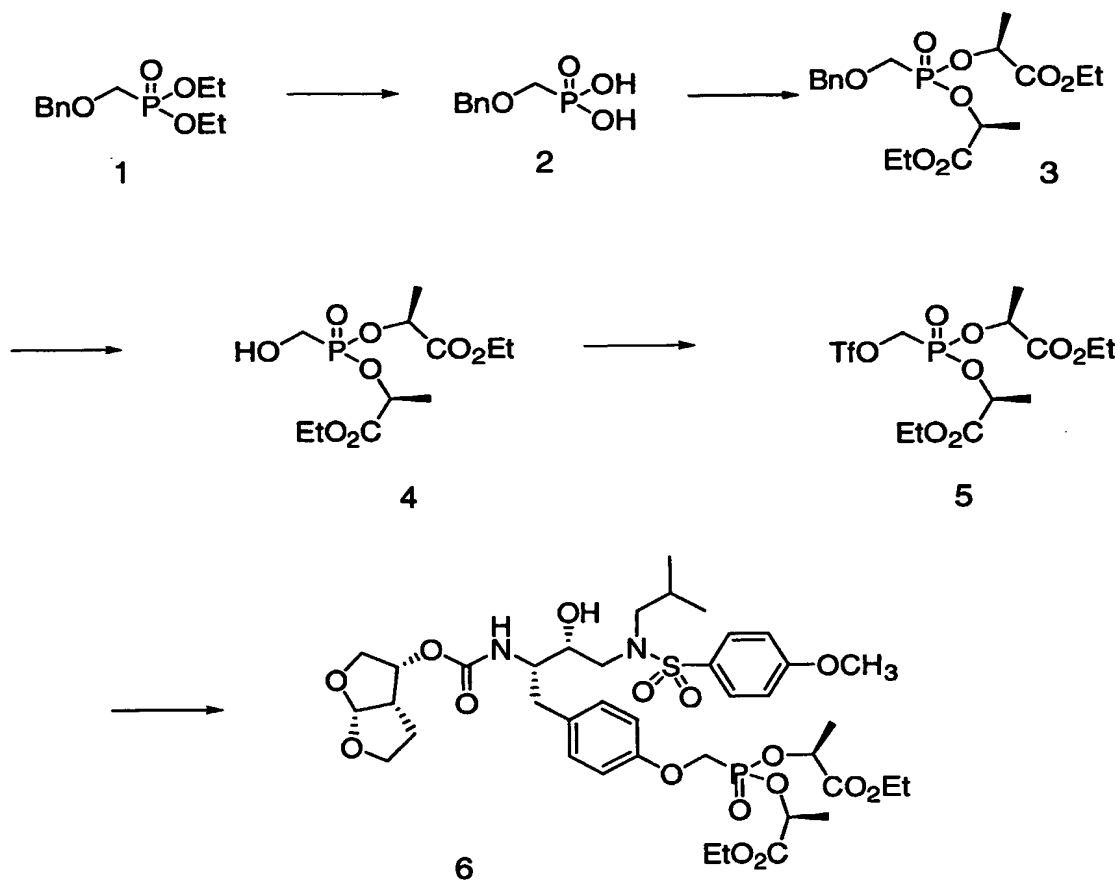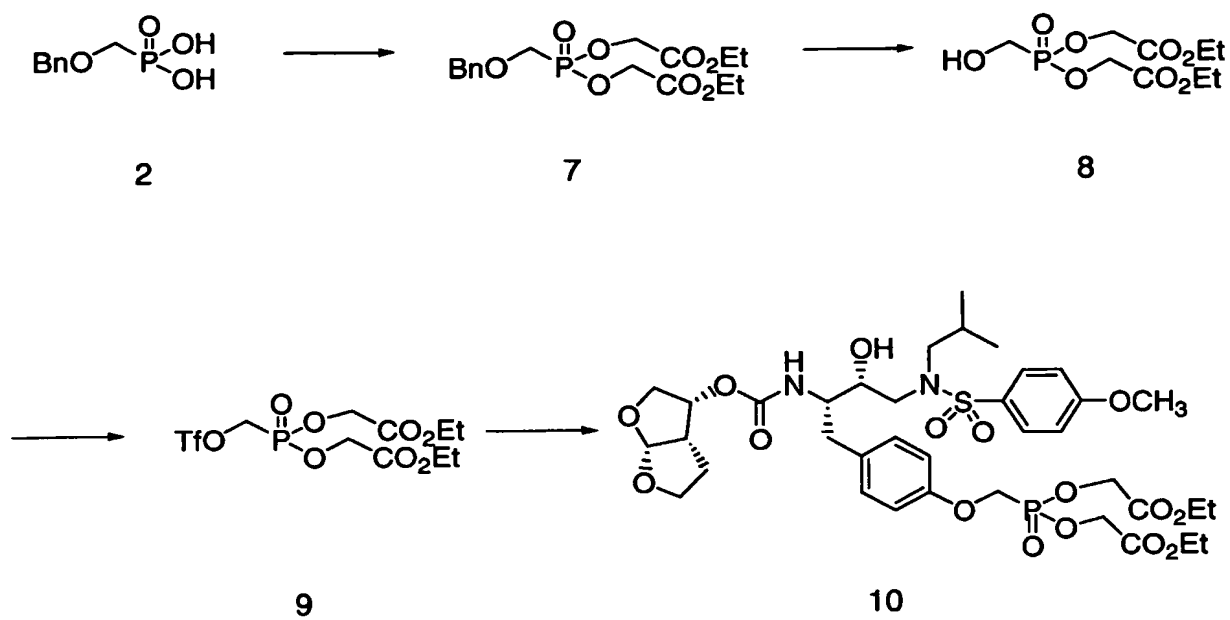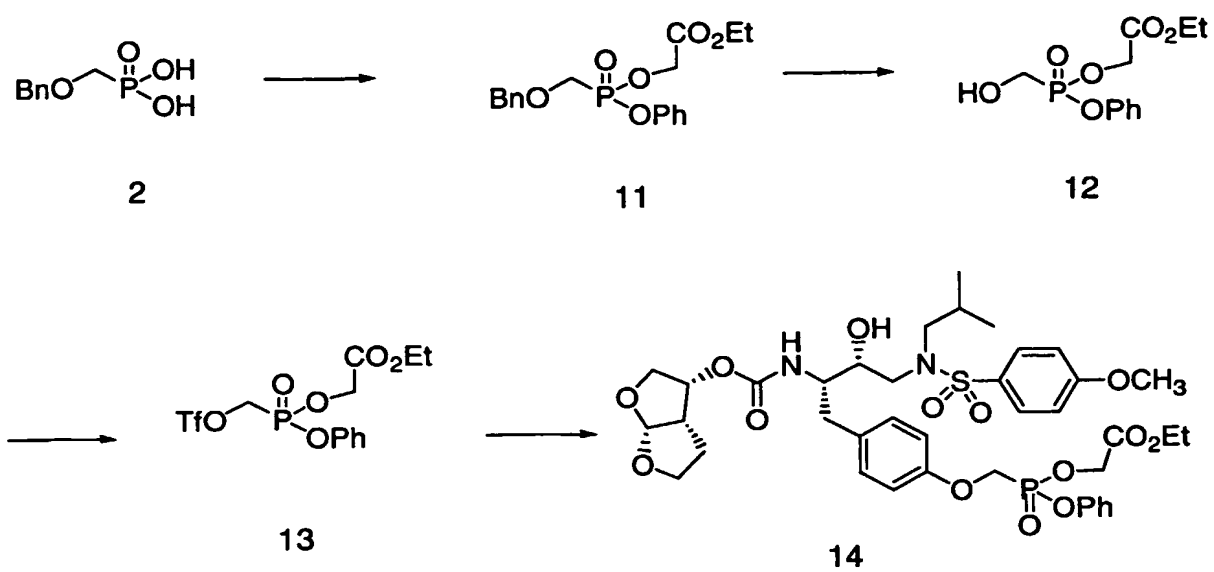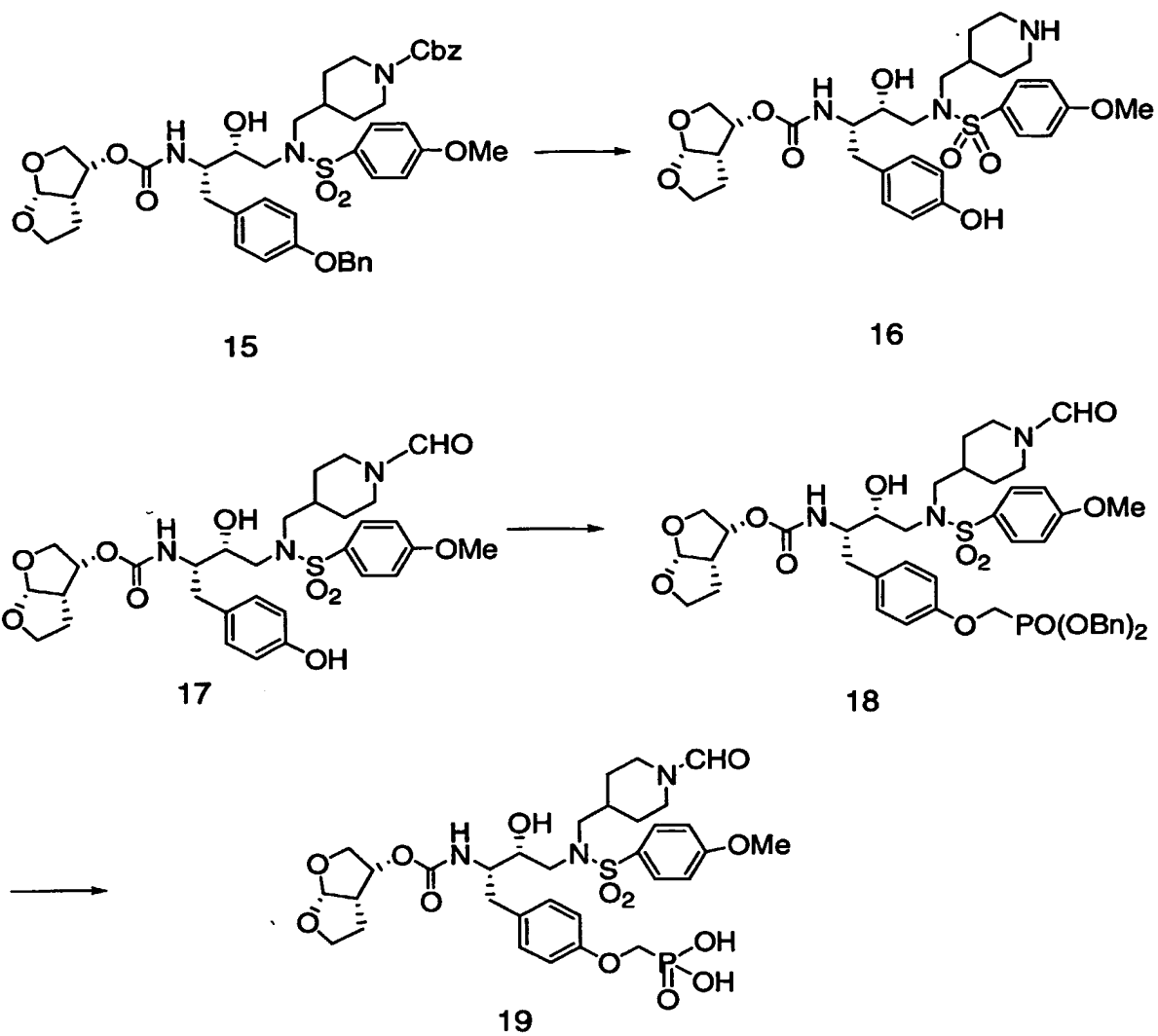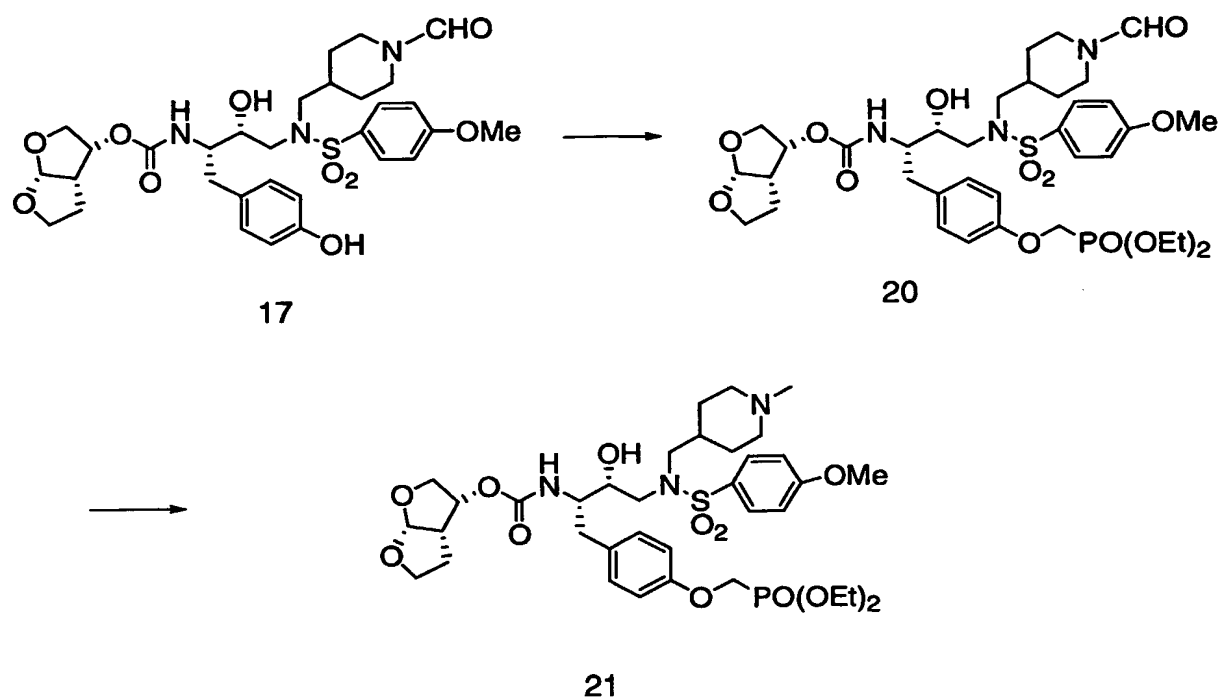
Scheme Section G

Schemes 1 to 9 are described in the examples.
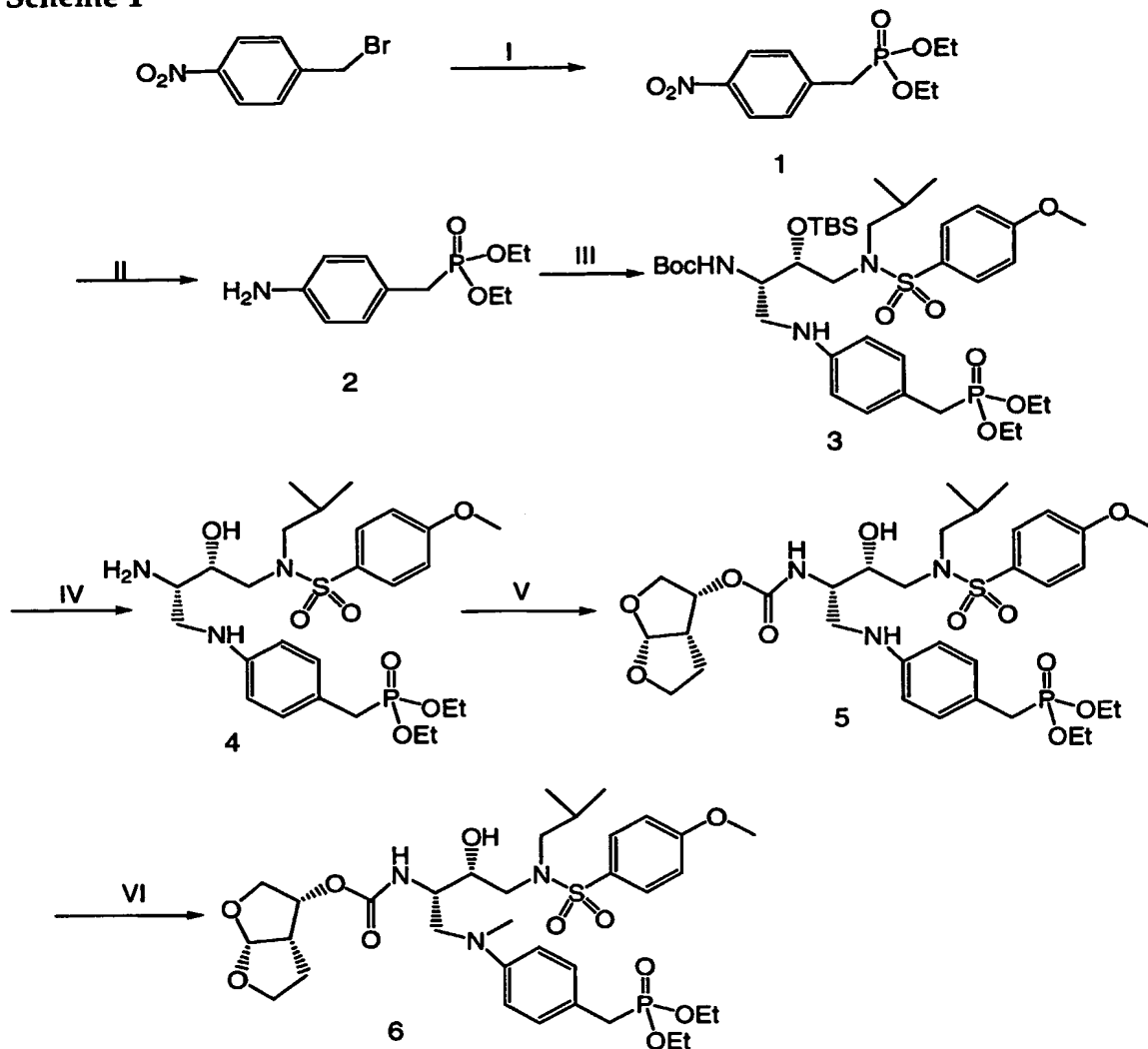
Scheme 1

I. P(OEt)$_3$/120 C; II. H$_2$/10%Pd-C; III. See Scheme Section H, Scheme 13, Compound 48 /NaBH$_3$CN/HOAc/MeOH; IV. a. TFA; b. n-Bu$_4$NF;V. bisfurancarbonate/DMAP; VI. HCHO/NaBH$_3$CN/HOAc/MeOH

5

Scheme 2

I. a.TMSBr; b. SOCl₂/60 C; c. BnOH/Et₃N; II. Zn/HOAc; III. See Scheme Section H, Scheme 13, Compound 48 /NaBH₃CN/HOAc/MeOH; IV. a. TFA; b. n-Bu₄NF; V. bisfurancarbonate/DMAP; VI. H₂/10%Pd-C; VIII.RNH₂/PPh₃/aldrithiol

Scheme 3
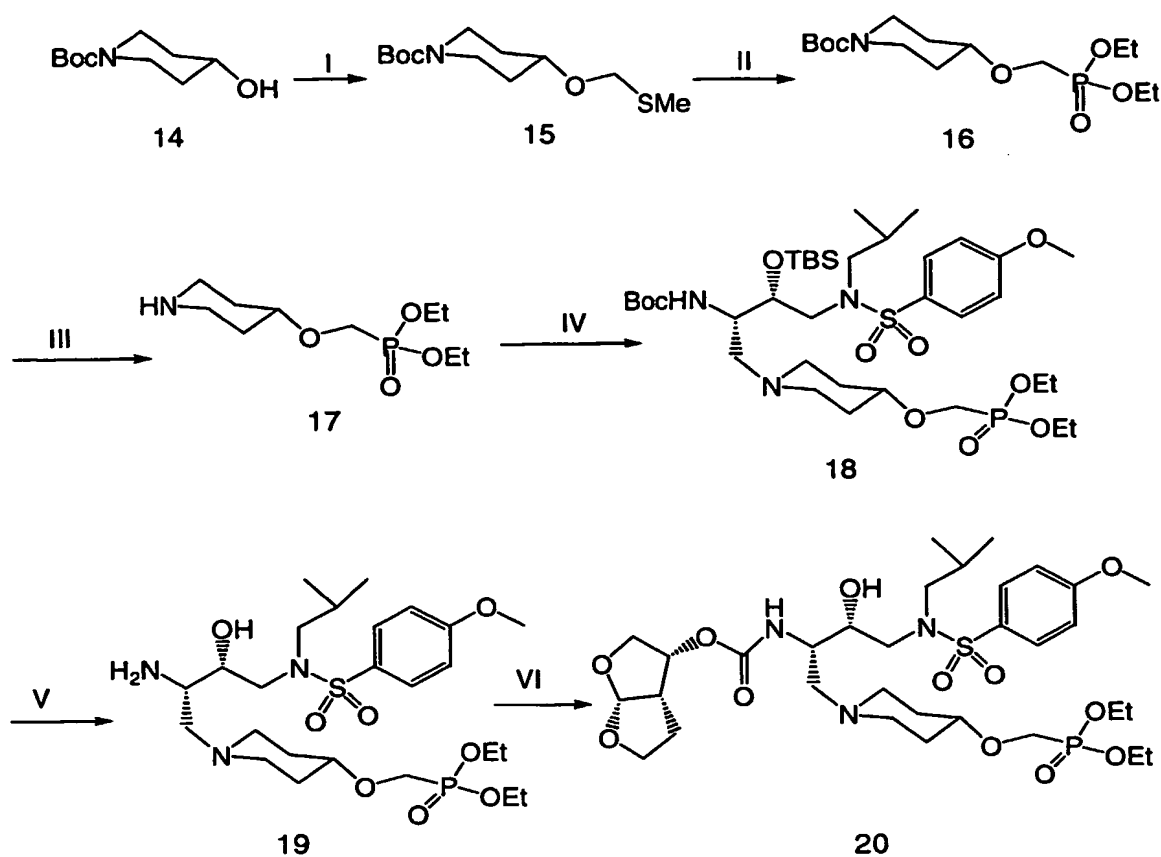
I. a. NaH; b. MTMCl; II. a. SOCl$_2$; b. P(OEt)$_3$/120 C; III. TFA; IV. See Scheme Section H, Scheme 13, Compound 48 /NaBH$_3$CN/HOAc/MeOH; V. a. TFA; b. n-Bu$_4$NF; VI. bisfurancarbonate/DMAP
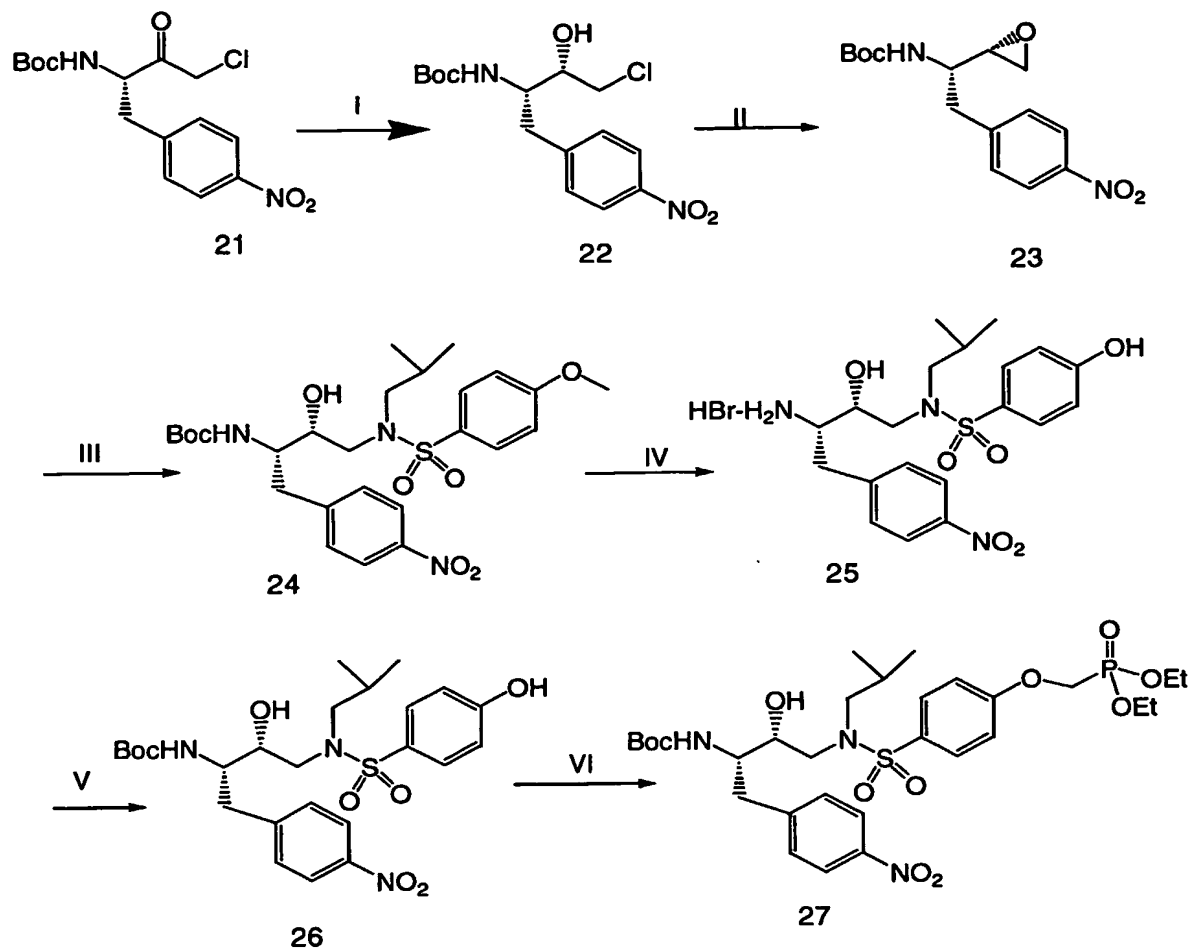
Scheme 4

I. NaBH$_4$/THF/H$_2$O ; II. KOH/EtOH; III. a. isobutylamine/iropropanol/80 C; b.
4-methoxybenzenesulfonyl chloride/Et$_3$N; IV.BBr$_3$/CH$_2$Cl$_2$; V. Boc$_2$O/NaHCO$_3$; VI.
TfOCH$_2$PO(OEt)$_2$/Cs$_2$CO$_3$

Scheme 5

27 ⟶

28

⟶

29

⟶

30
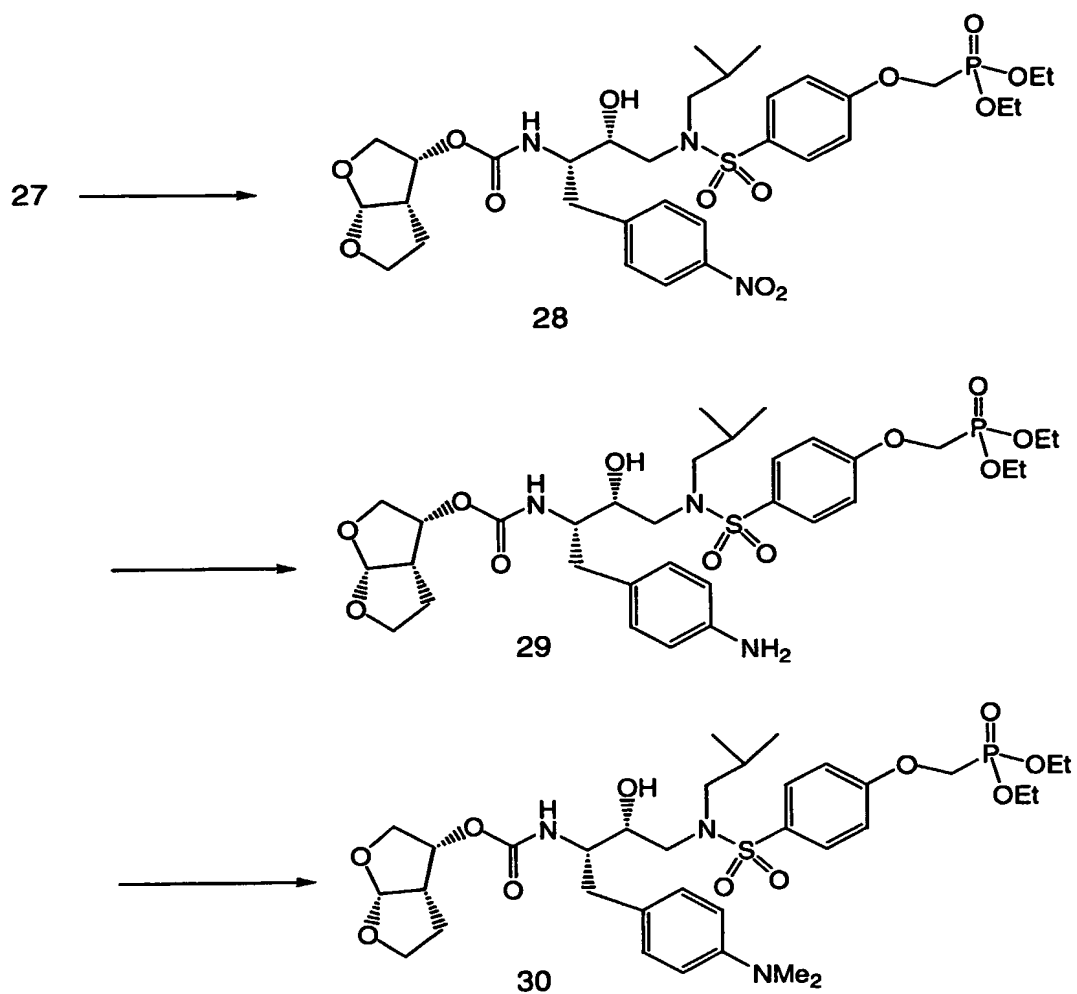
I. TFA/CH₂Cl₂; b. bisfurancarbonate/DMAP ; II. H₂/10% Pd-C/EtOH;
III. HCHO/NaBH₃CN/HOAc/MeOH

Scheme 6
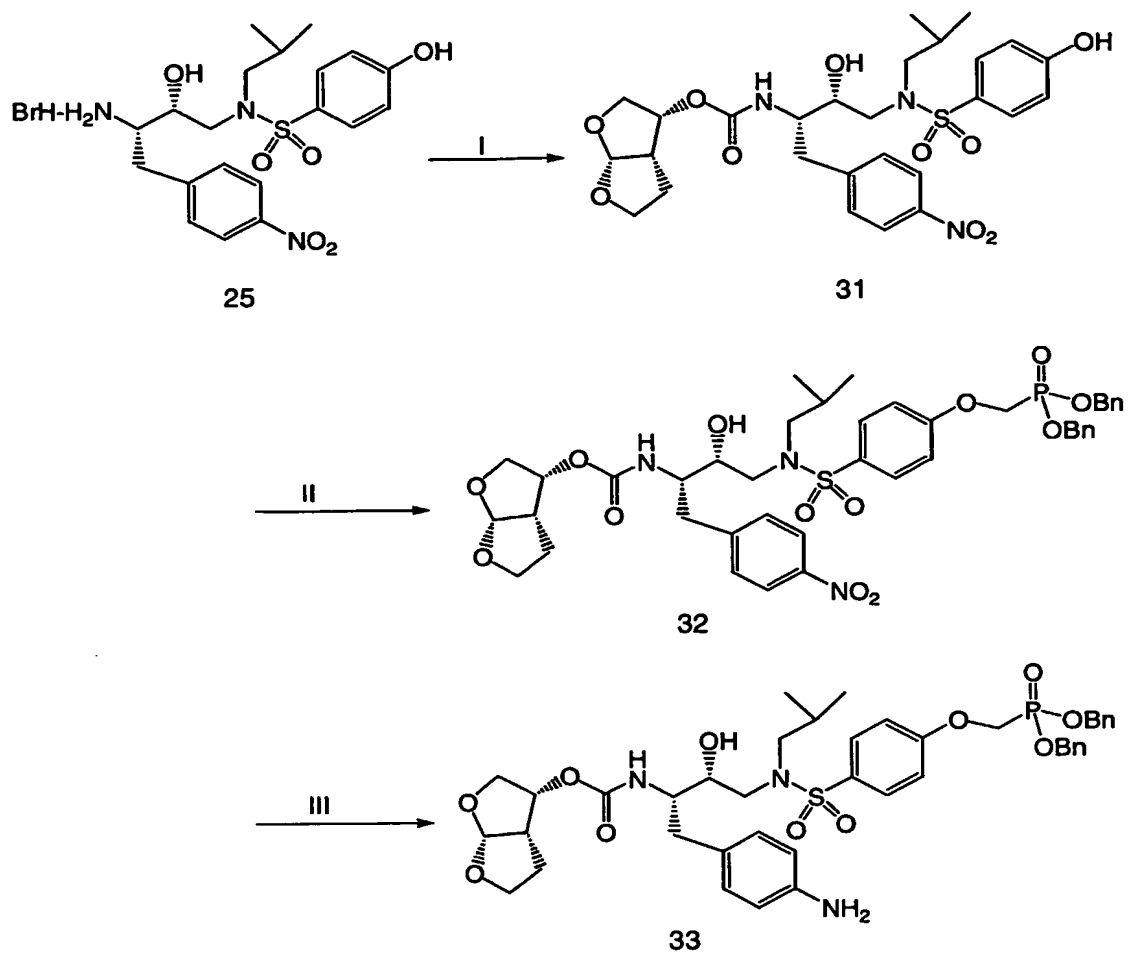
I.a. TMSCl/Et$_3$N; b. bisfurancarbonate/DMAP; c. n-Bu$_4$NF/HOAc; II. TfOCH$_2$PO(OBn)$_2$/Cs$_2$CO$_3$; III. Zn/HOAc

Scheme 7
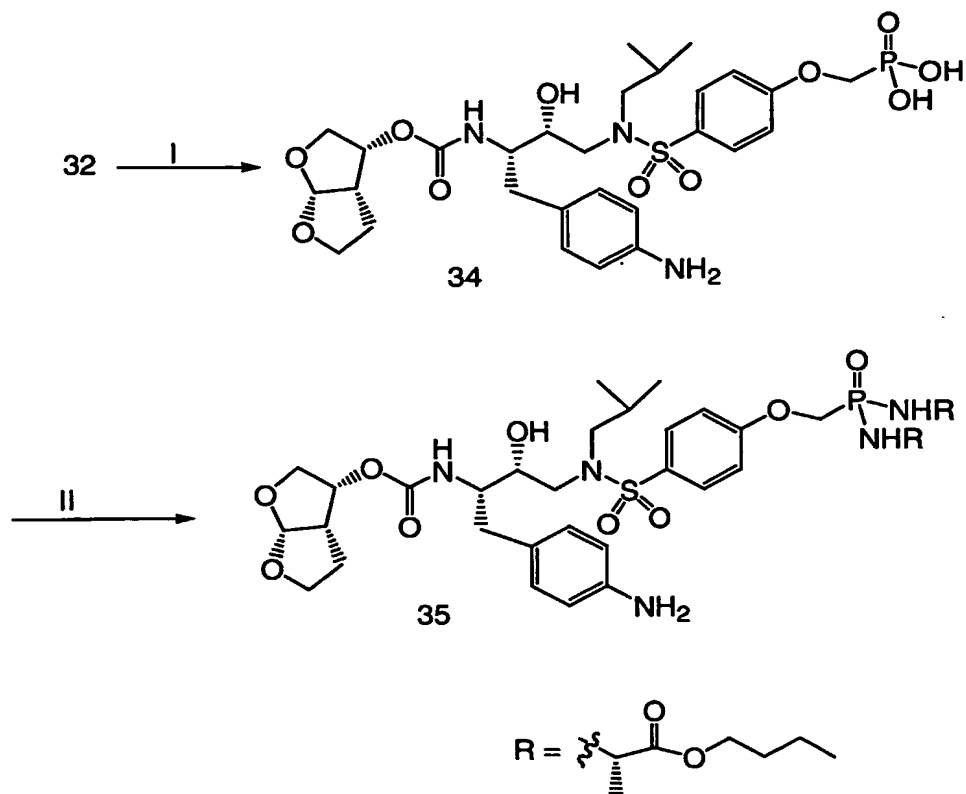
I. H₂/10% Pd-C; II. RNH₂/PPh₃/Aldrithiol/diisopropylethylamine/pyridine

Scheme 8

36

I. RNH₂/PPh₃/Aldrithiol/diisopropylethylamine/pyridine

37 R =

38 R =

39 R =
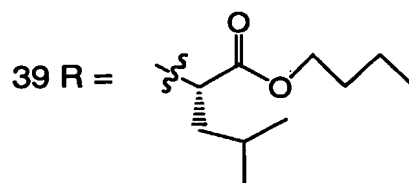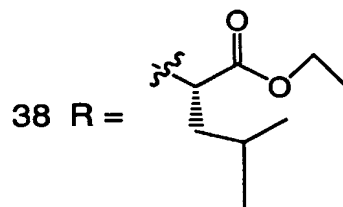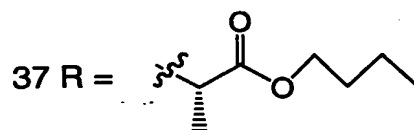
Scheme 9

I. RNH₂/PPh₃/Aldrithiol/diisopropylethylamine/
pyridine

41 R =

42 R =
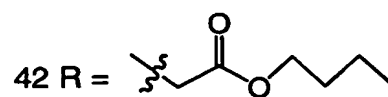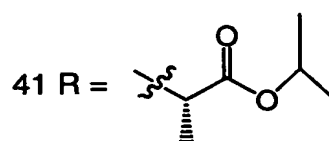
Scheme Section H

Schemes 1-14 are described in the examples.

Scheme 1

Scheme 2

(1) BSA, CN₃CN, 70°C

(2) CBzCl, Py, 0°C to r.t.

7

DCC, PhOH

Py, 70°C

8

NaOH, CH₃CN

9
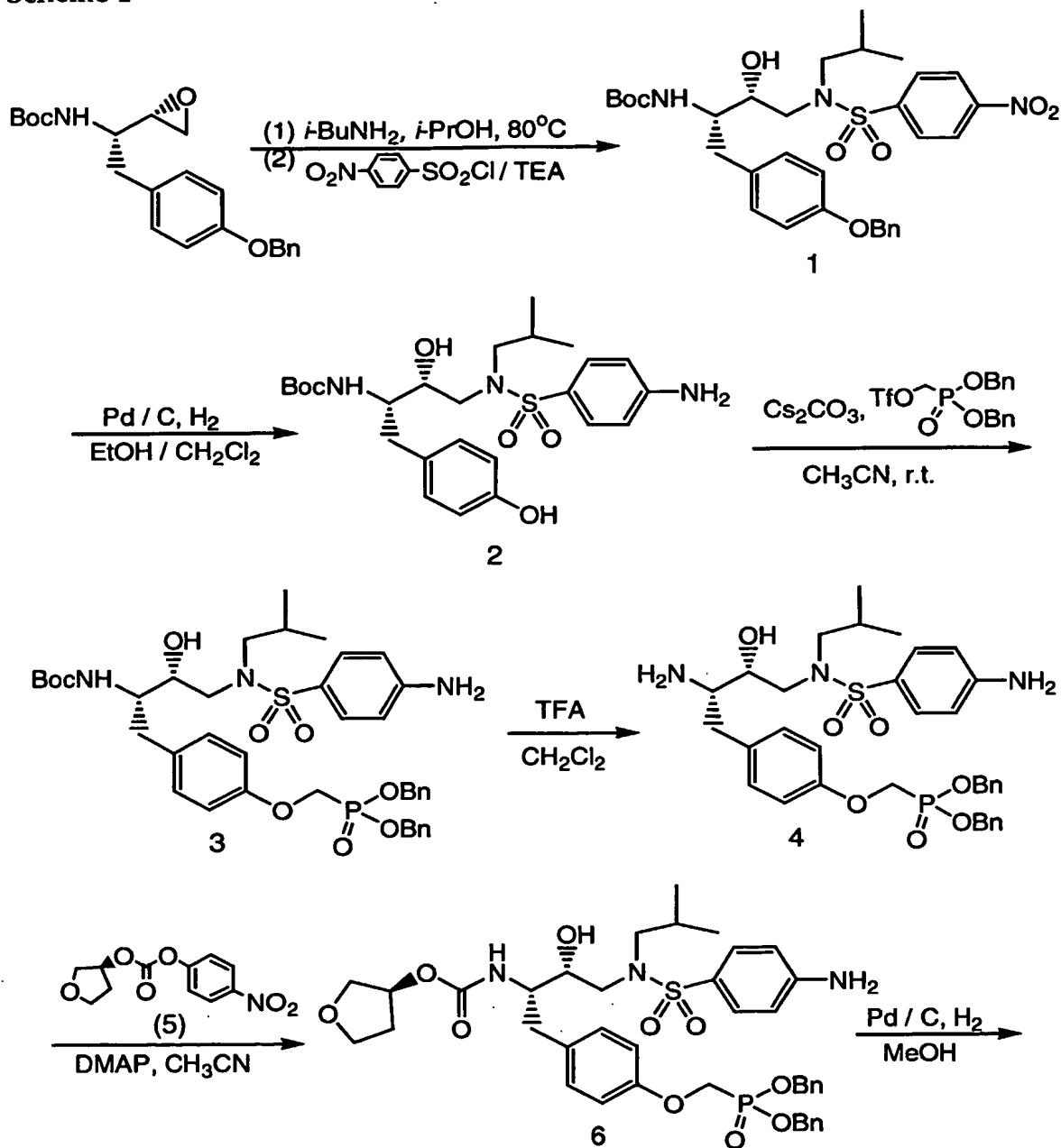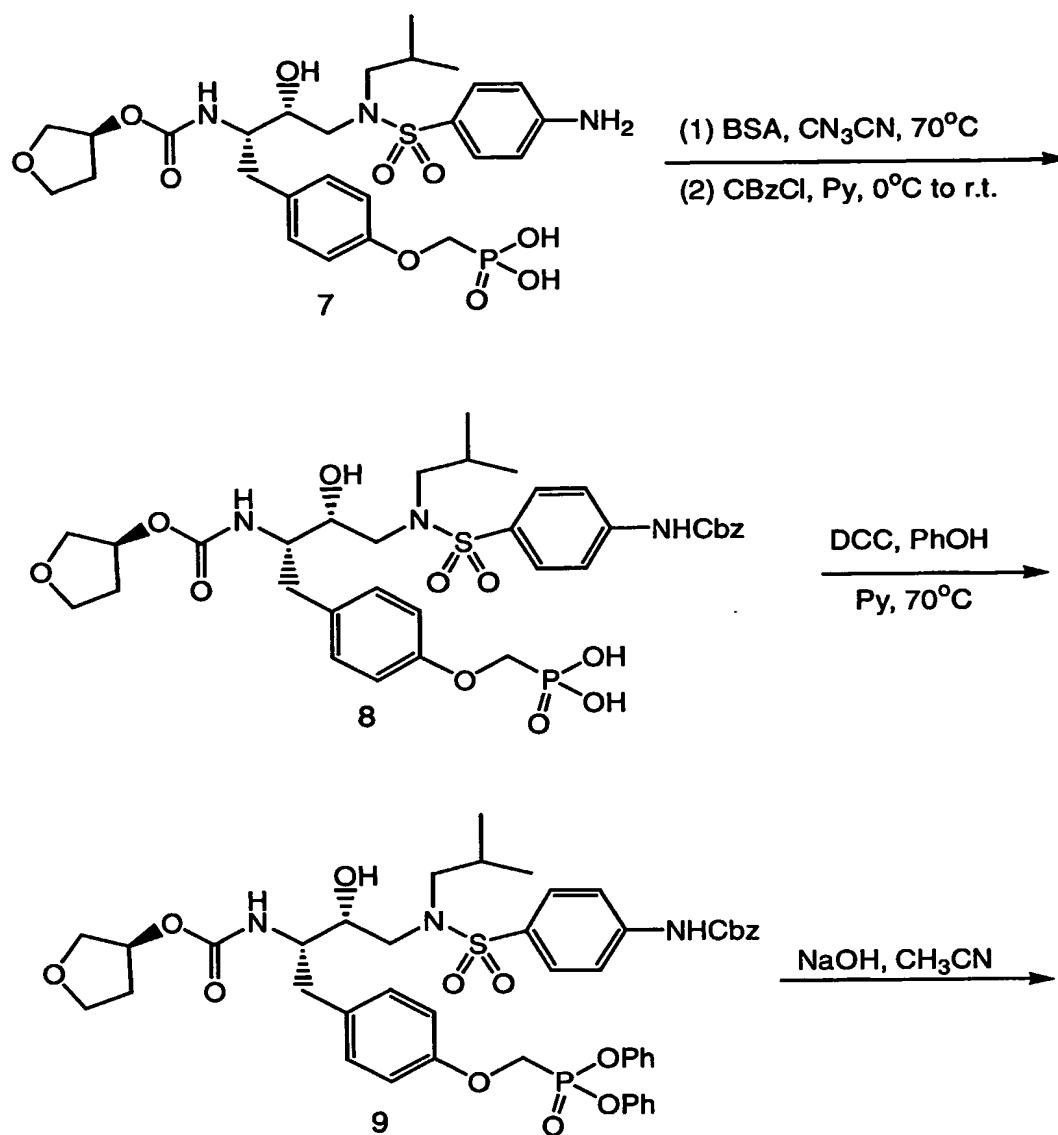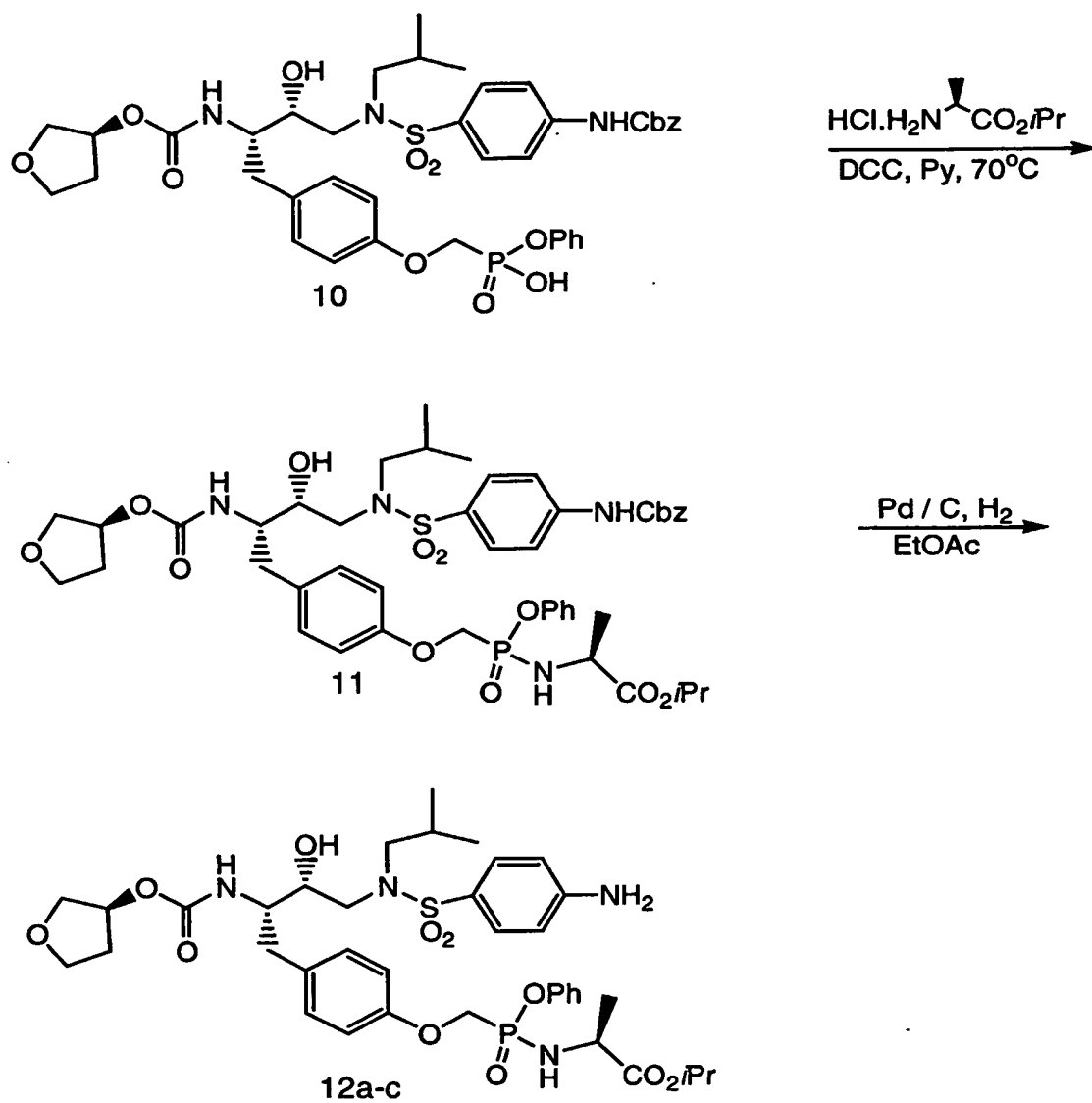
Scheme 3

12a, GS 108577 (isomer A / B = 1 : 1)
12b, GS 108578 (isomer A)
12c, GS 108579 (isomer B)

Scheme 4

Scheme 5

16

DMAP, CH₃CN

17

Zn, HOAc

18

10% Pd / C, H₂

MeOH / HOAc

19
GS 17424

Scheme 6

(1) TMSCl, TEA, CH_2Cl_2
(2) Boc_2O, TEA, CH_2Cl_2

(3) 1.0 M TBAF / HOAc, THF

20

21

Cs_2CO_3, TfO—CH₂—P(=O)(OBn)(OBn)
THF, r.t.

22

TFA, CH_2Cl_2

23

DMAP, CH_3CN

Scheme 7

24

Pd / C, H₂ → EtOH

25

(1) BSA, CN₃CN, 70°C → (2) CBzCl, Py, 0°C to r.t.

26

DCC, PhOH → Py, 70°C

27

NaOH, CH₃CN →

Scheme 8

HCl.H$_2$N CO$_2$iPr

DCC, Py, 70°C

28

Pd / C, H$_2$

EtOH

29

30 a-b

30a   R = H, GS 77369
30b   R = Et, GS 77425

Scheme 9

31

32
GS 17389

Scheme 10

Scheme 11

36

(1) MsCl, TEA
   THF / CH$_2$Cl$_2$

(2) LiBr, 45 min

37

P(OEt)$_3$, toluene

120°C, overnight

38

GS 191338

Scheme 12

BocNH—...—OH with OH side chain

$\xrightarrow[\text{DMF}]{\text{BnBr,NaH}}$

BocNH—...—OH with OBn side chain

39

$\xrightarrow[\text{(2) CH}_2\text{N}_2]{\text{(1) }i\text{-BuOCOCl / NMM}}$

BocNH—...—(C=O)—CH=N$_2$ with OBn side chain

40

$\xrightarrow{\text{HCl in dioxane}}$

BocNH—...—(C=O)—CH$_2$Cl with OBn side chain

41

$\xrightarrow[\text{(9:1)THF / H}_2\text{O}]{\text{NaBH}_4}$

BocNH—...—CH(OH)—CH$_2$Cl with OBn side chain

42

$\xrightarrow{\text{KOH, EtOH}}$

BocNH—...—epoxide with OBn side chain

43

$+$

BocNH—...—epoxide with OBn side chain

44

Scheme 13

43

(1) isobutylamine

(2) MeO—⟨ ⟩—SO₂Cl / TEA

45

TBSOTf / TEA
——————————
CH₂Cl₂

46

Pd / C, H₂
——————————

47

Dess-Martin
——————————

48

Scheme 14

Scheme Section I

Schemes 1 to 3 are described in the examples.

Scheme 1

1

3

4

5

GS16573

Scheme 2

4

Cs$_2$CO$_3$, TfO$\frown$P(OBn)(OBn), O
THF, r.t.

6
GS16574

Pd / C, H$_2$
EtOH

7
GS16575

Scheme 3

1

9

10
GS17089

11
GS17090
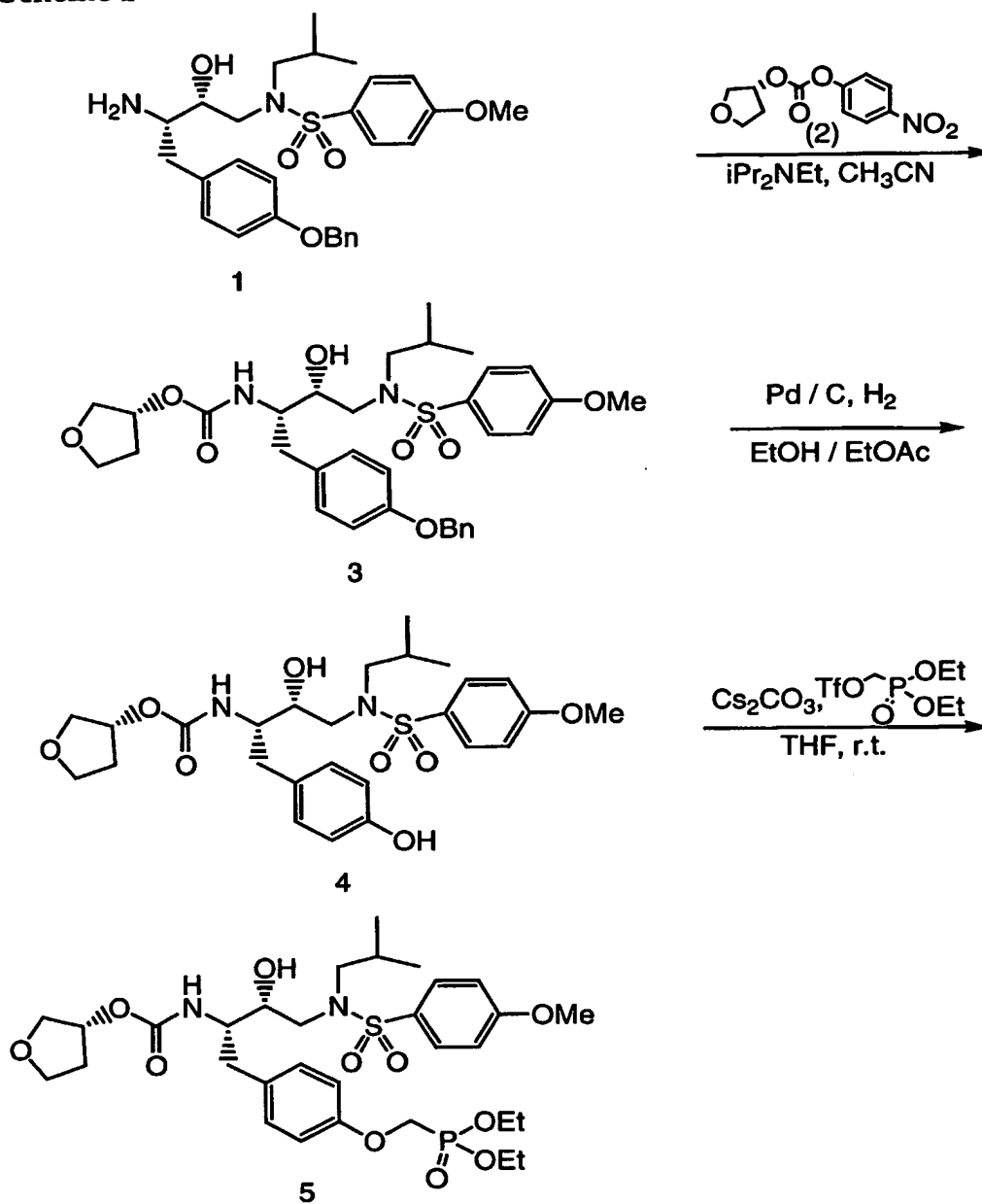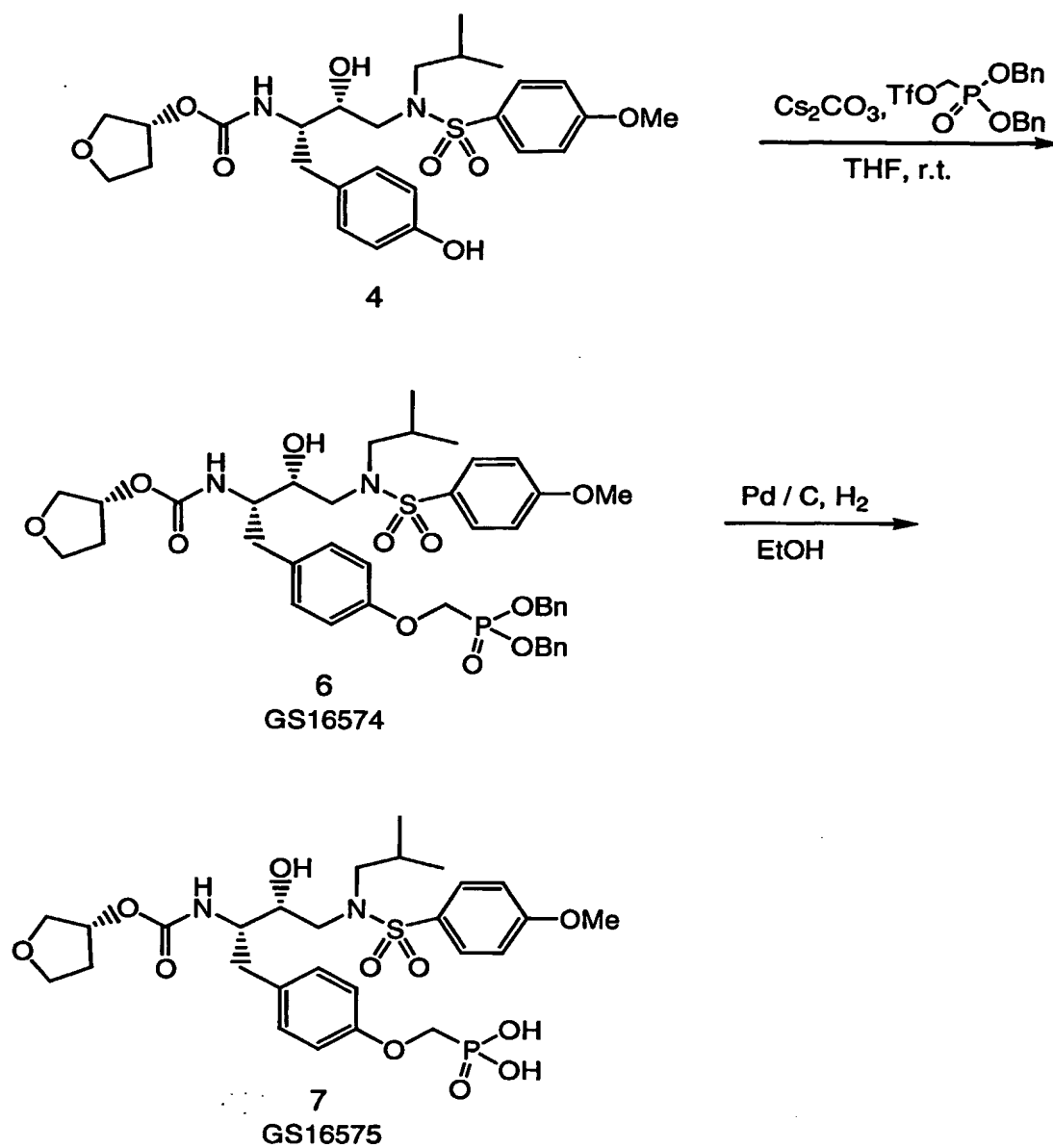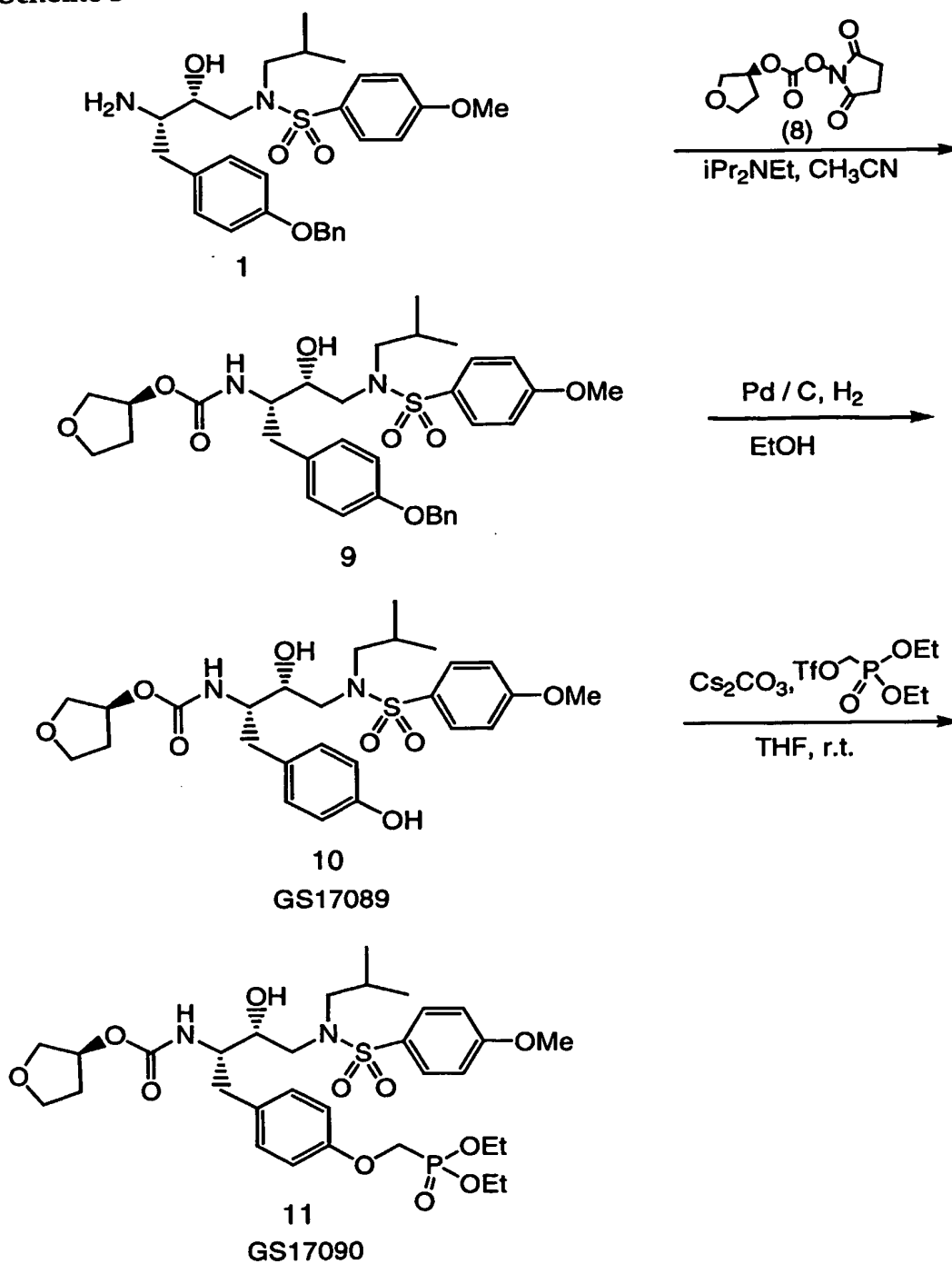
Scheme Section I

Schemes 1-4 are described in the examples.

Scheme 1

A

1

2

3   3a-e

Scheme 2

Scheme 3

A

1

2

3a : R = -Bn
3b : R = -Et

4a : R = -Bn
4b : R = -Et

5a : R = -Bn
5b : R = -Et

6

Scheme 4

3b

7

8
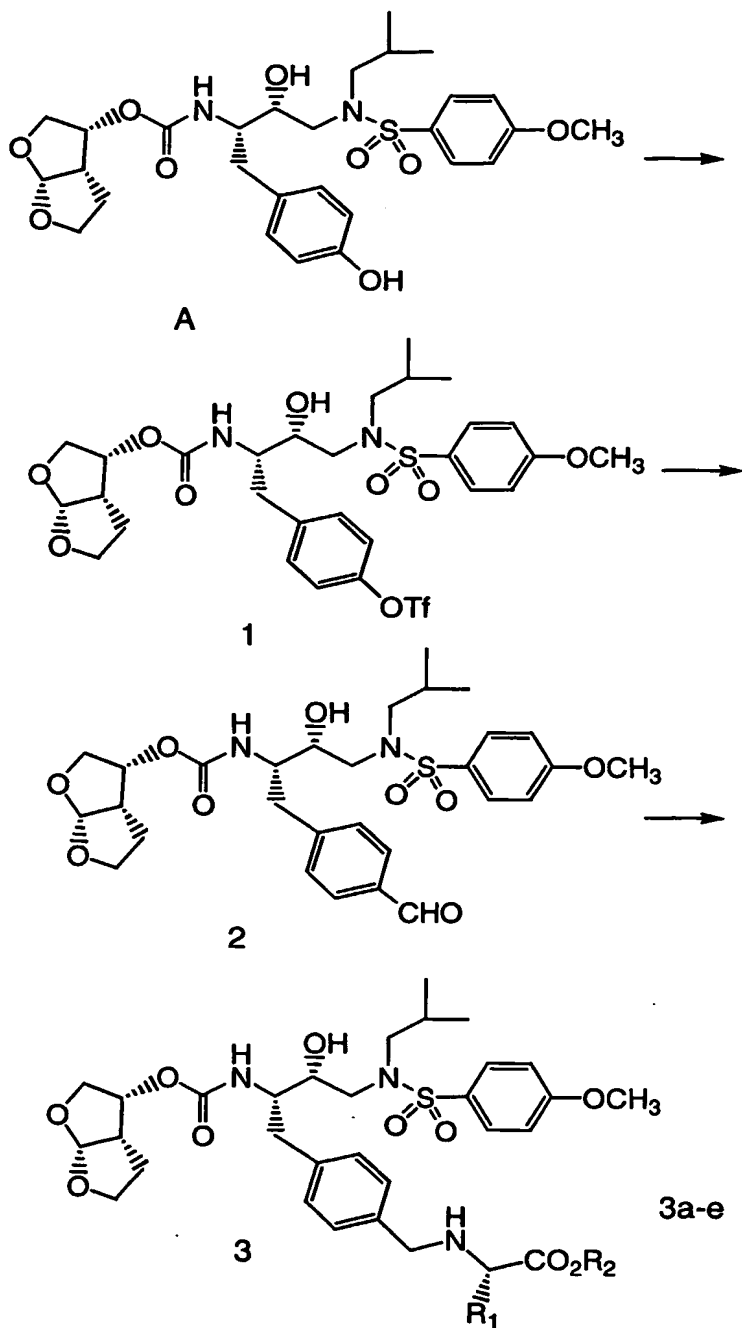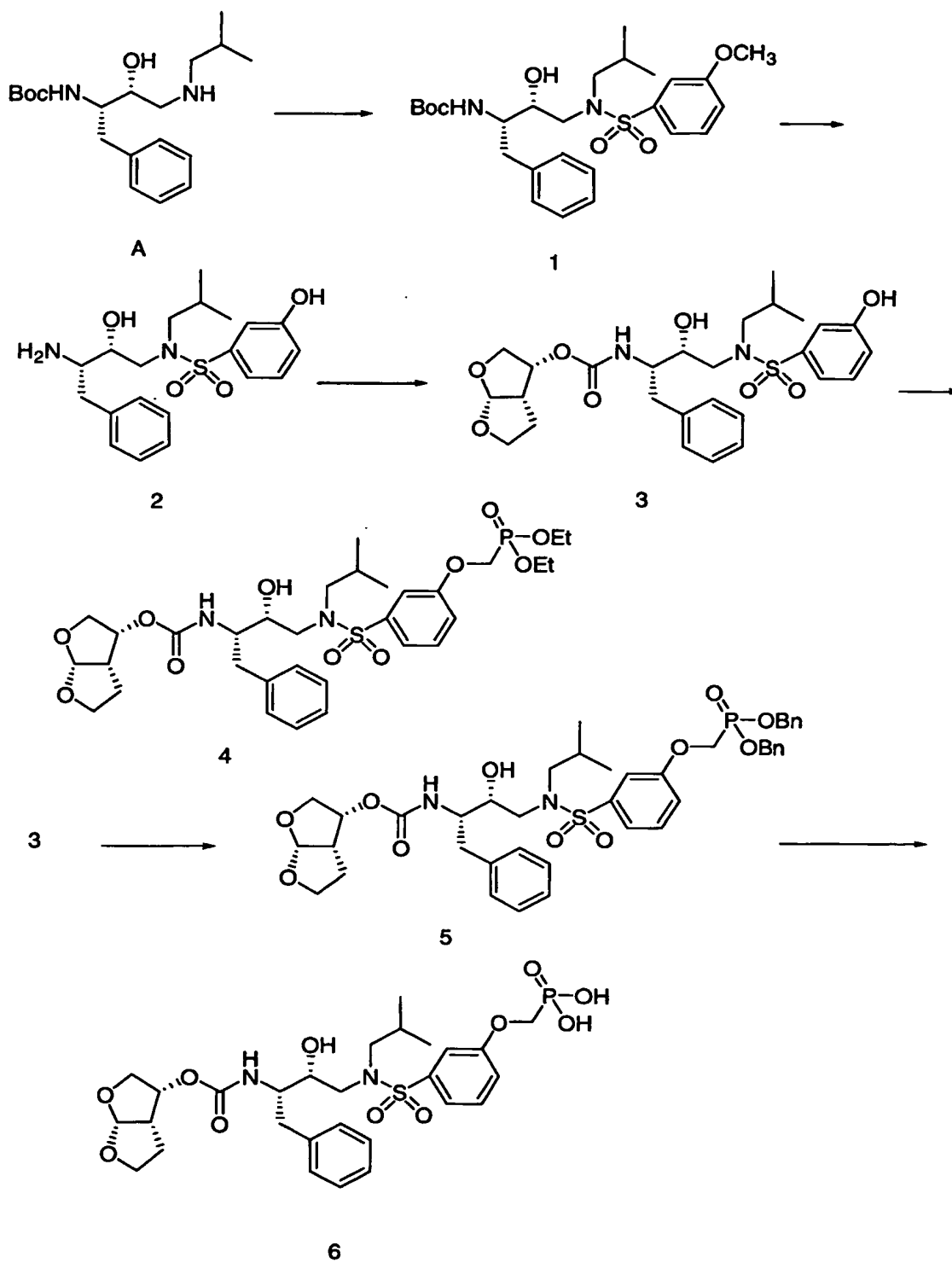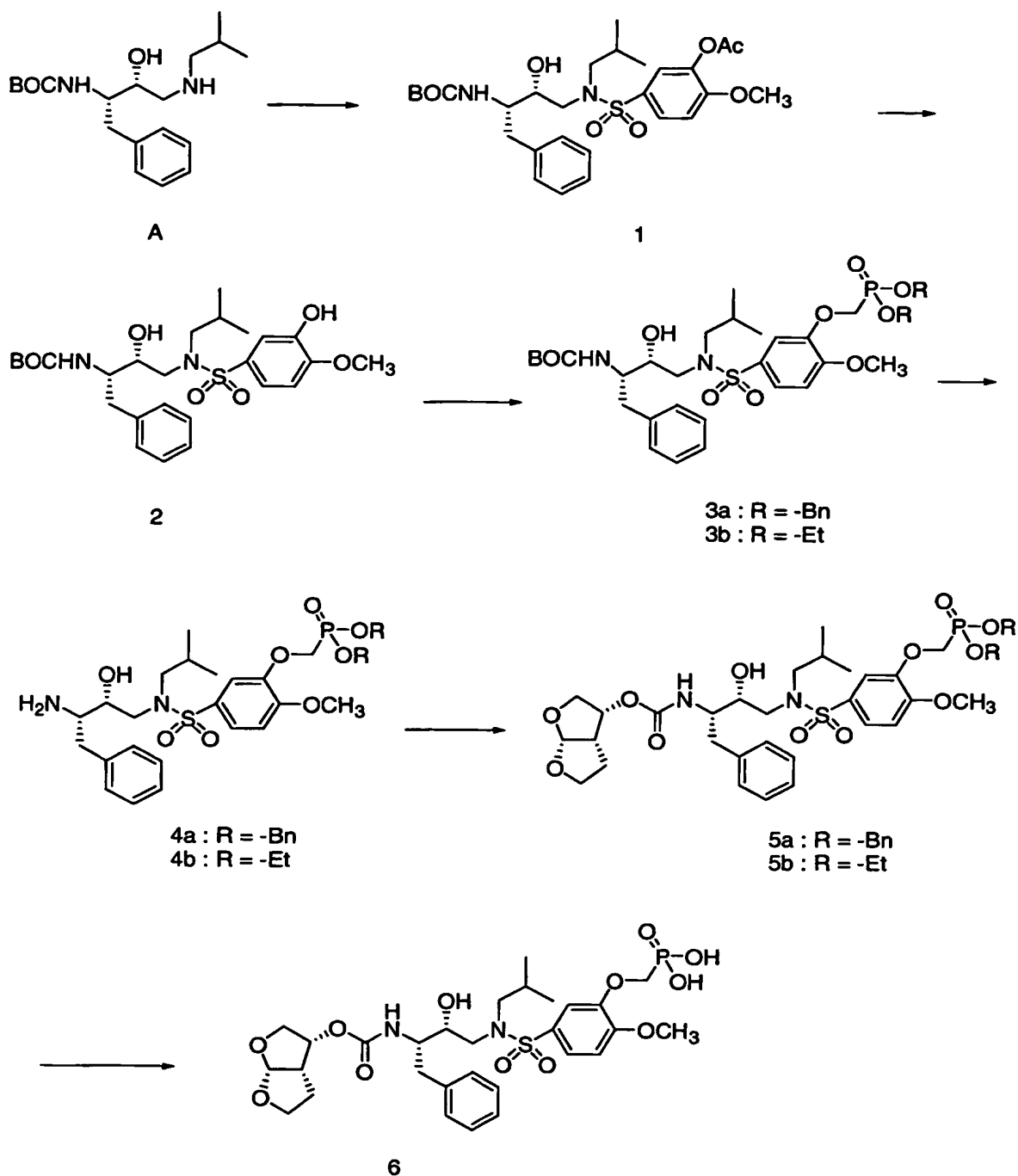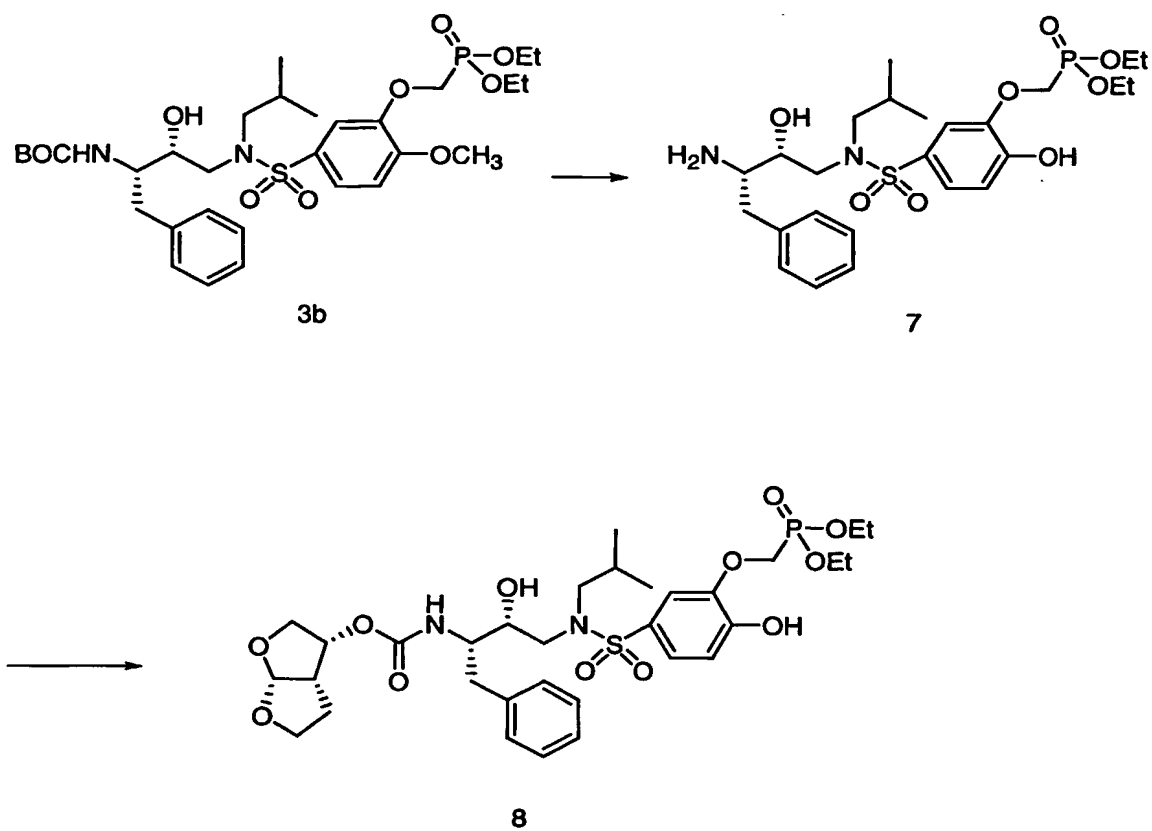
Scheme Section K

Schemes 1-9 are described in the examples.

5   **Scheme 1**

Scheme 2

!0

Scheme 3

6

+

HCl • H₂N

7

Ph₃P, (Pr)₂NEt
r.t., 20 hrs.

8

Scheme 4

5

9

10% Pd/C, H₂
EtOH/EtOAc, r.t.

6

Scheme 5

6

Phenol, DCC

70°C, pyridine

10

5

Scheme 6

10

NaOH (1N)

0°C, acetonitrile
Dowex H⁺

1
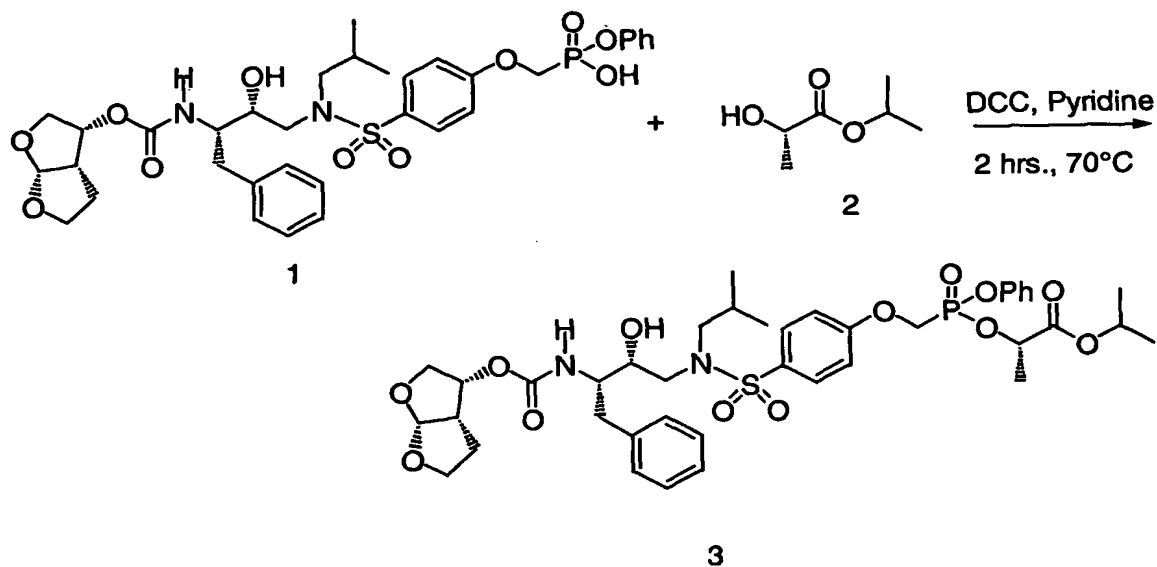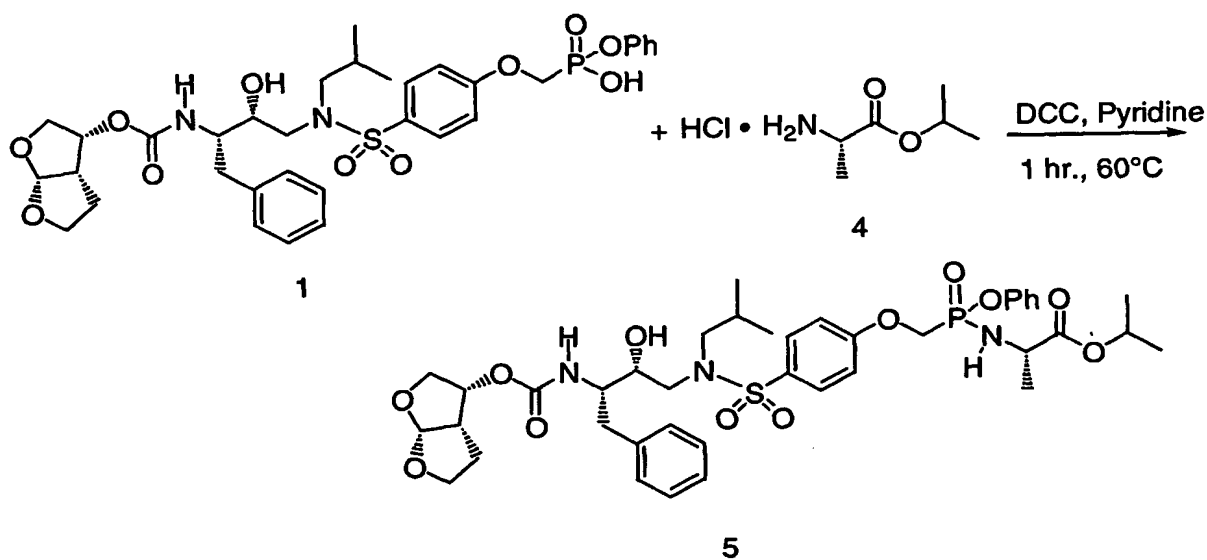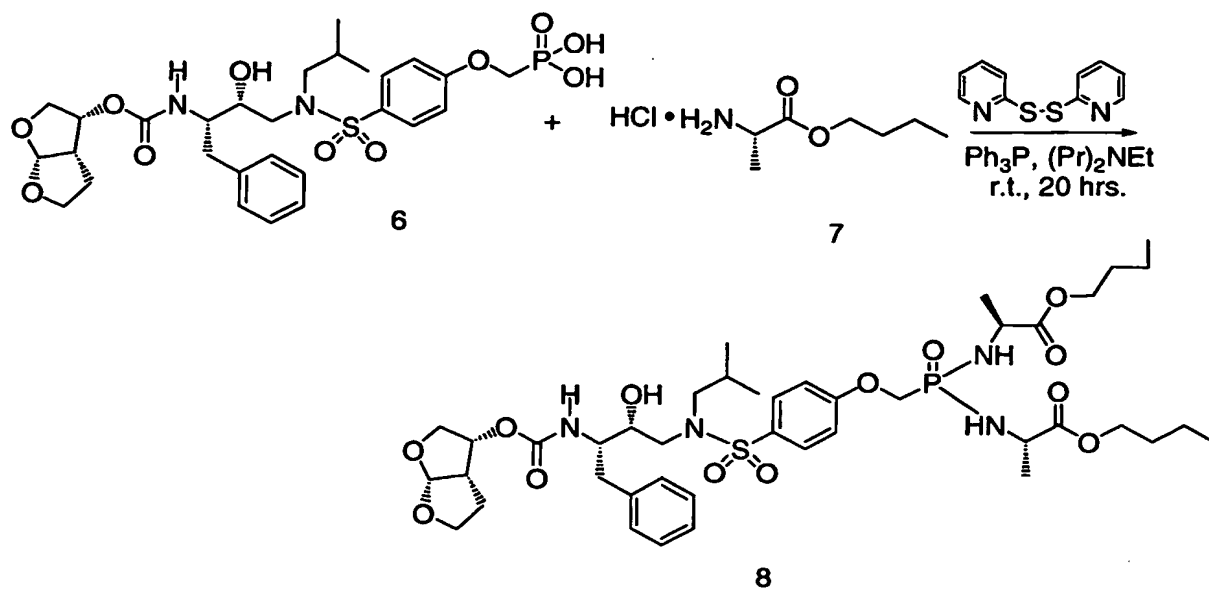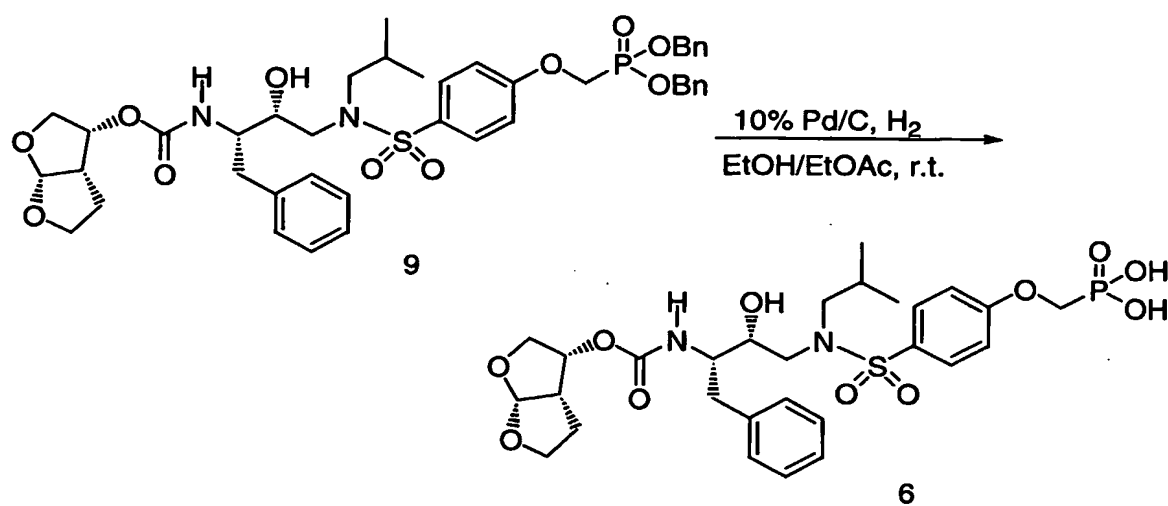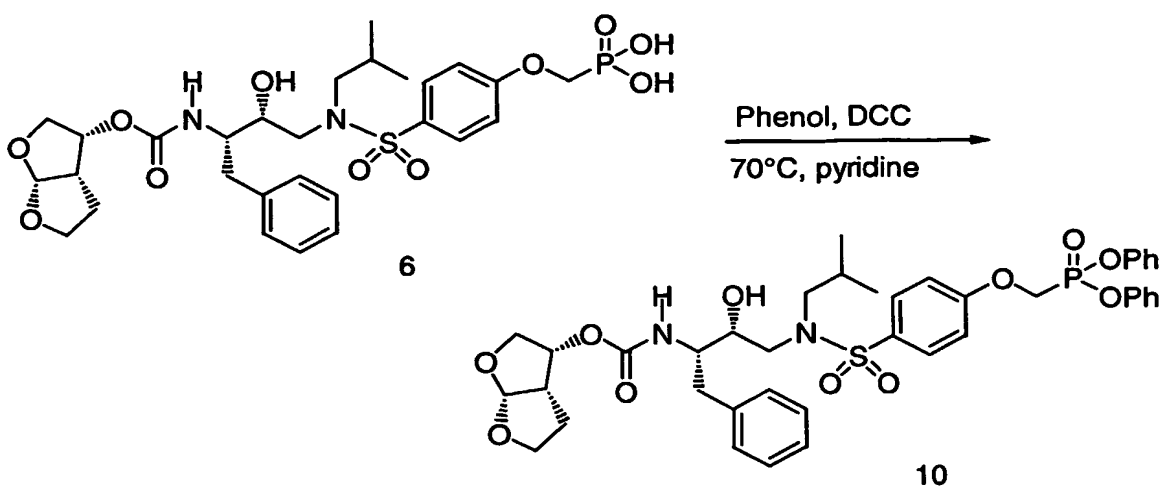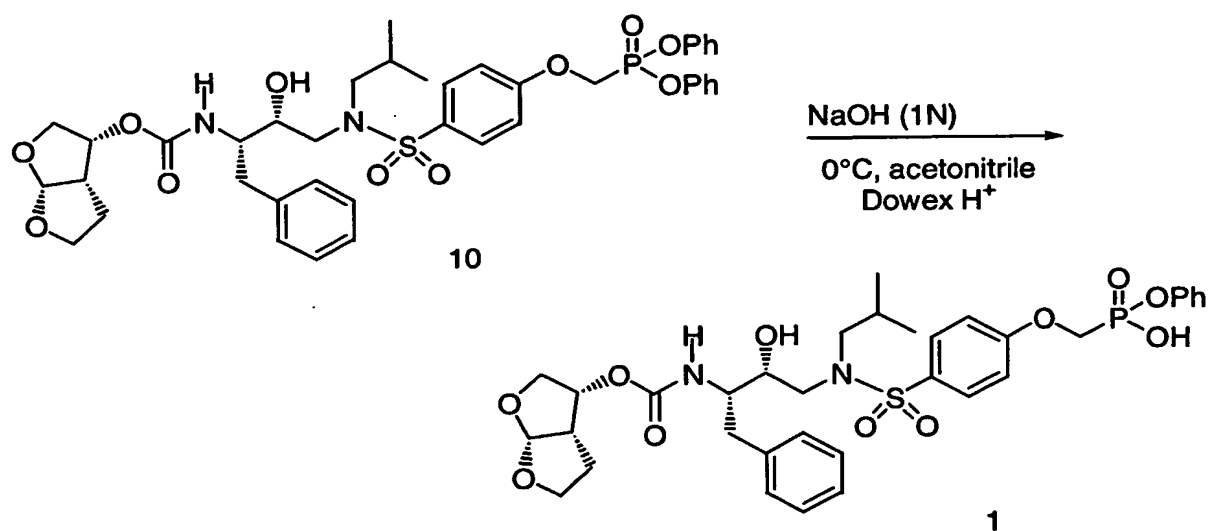
Scheme 7

5   **Scheme 8**

Scheme 9

14　　　　　　　　+　　　　　　　　15

DMAP
CH₃CN, r.t.

16

5
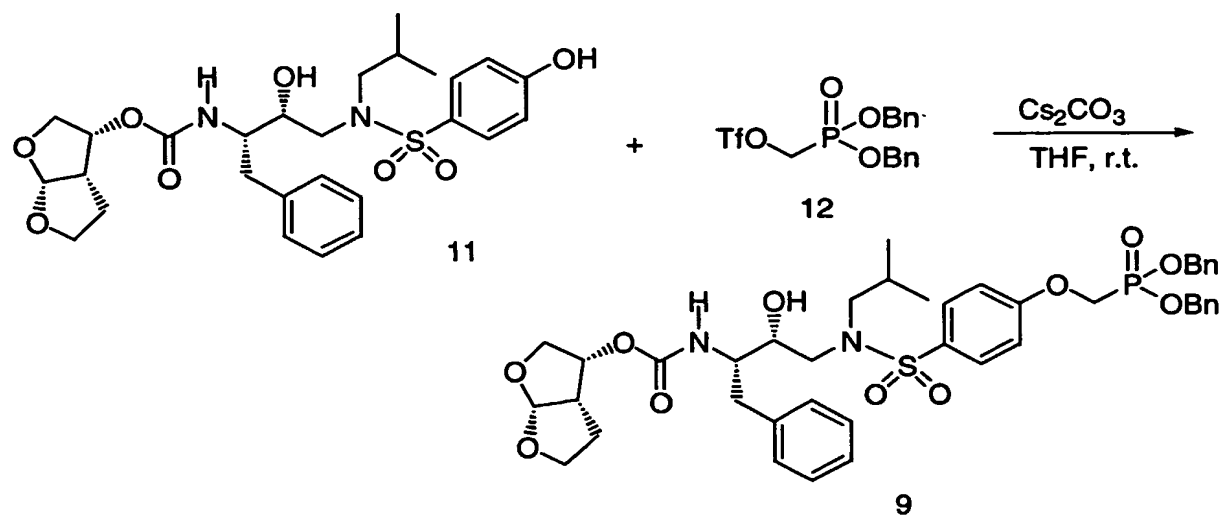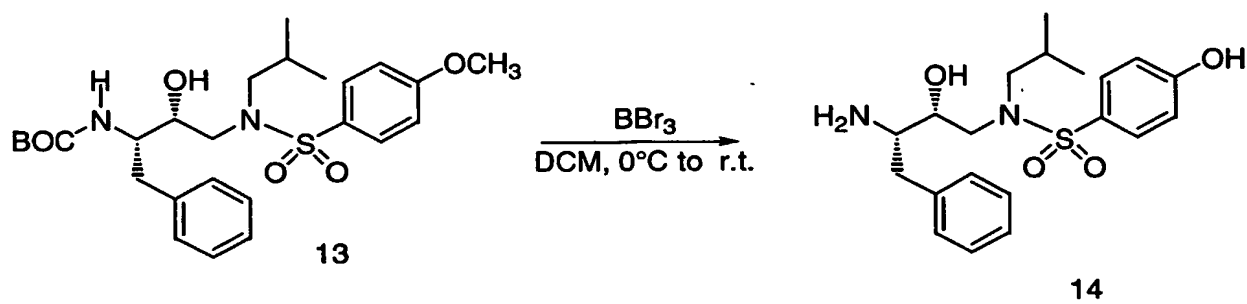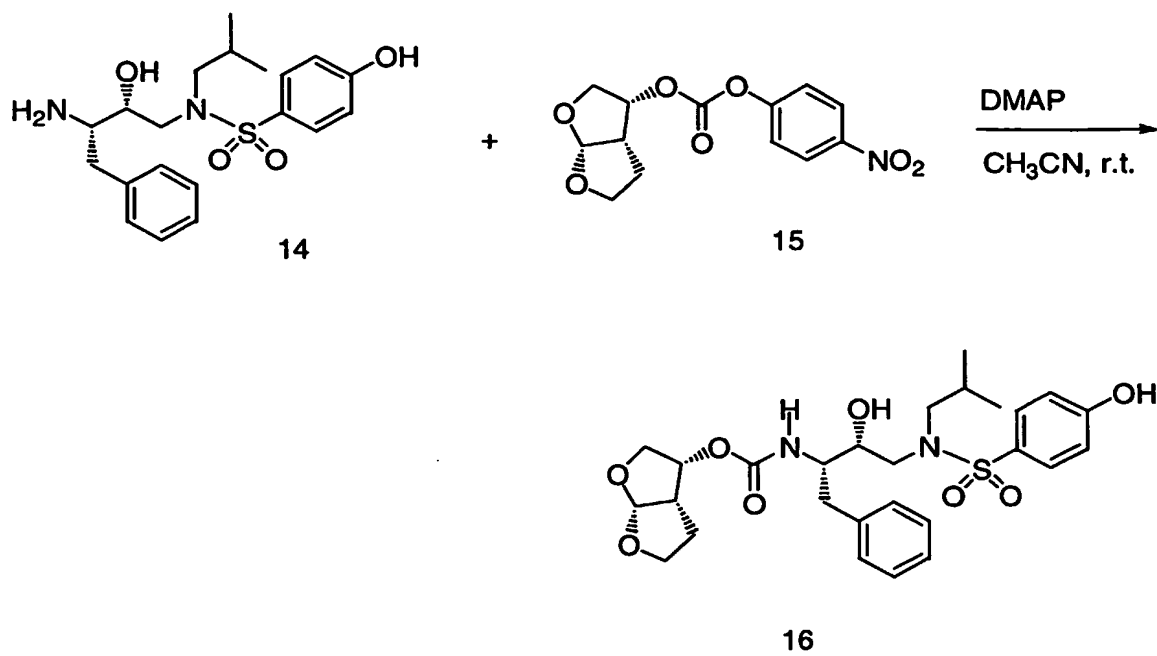
Scheme Section L

Schemes 1-9 are described in the examples.

Scheme 1

Synthesis of P1-Phosphonic ester

1

2

3

4

5

Scheme 2

11

5
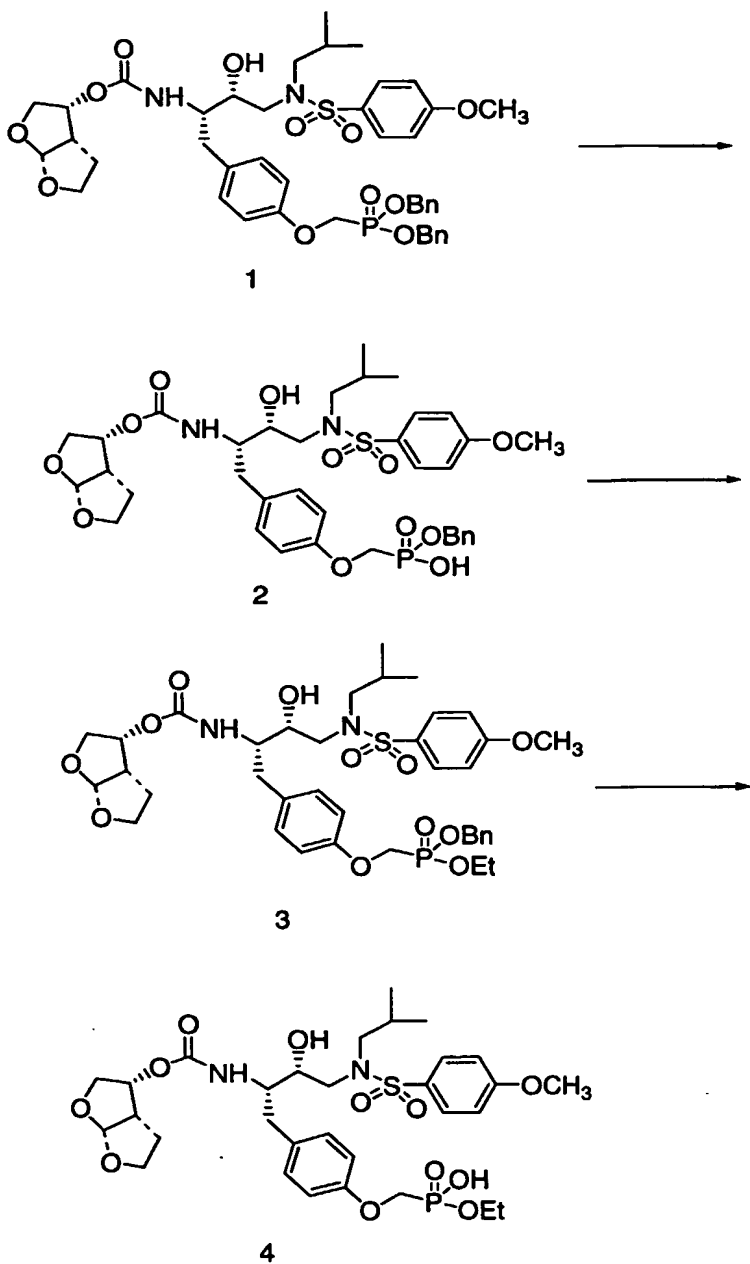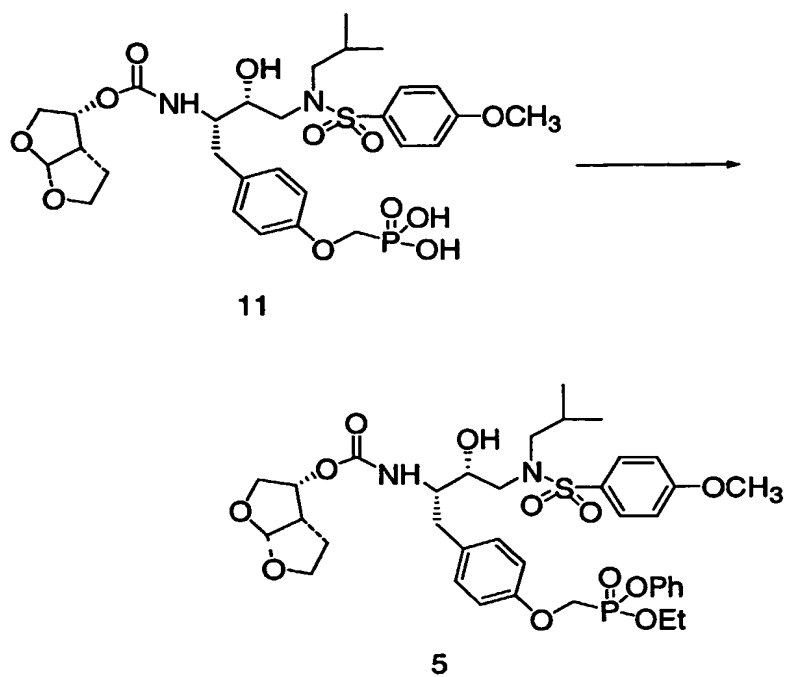
Scheme 3

Synthesis of P2'-Amino-P1-Phosphonic ester
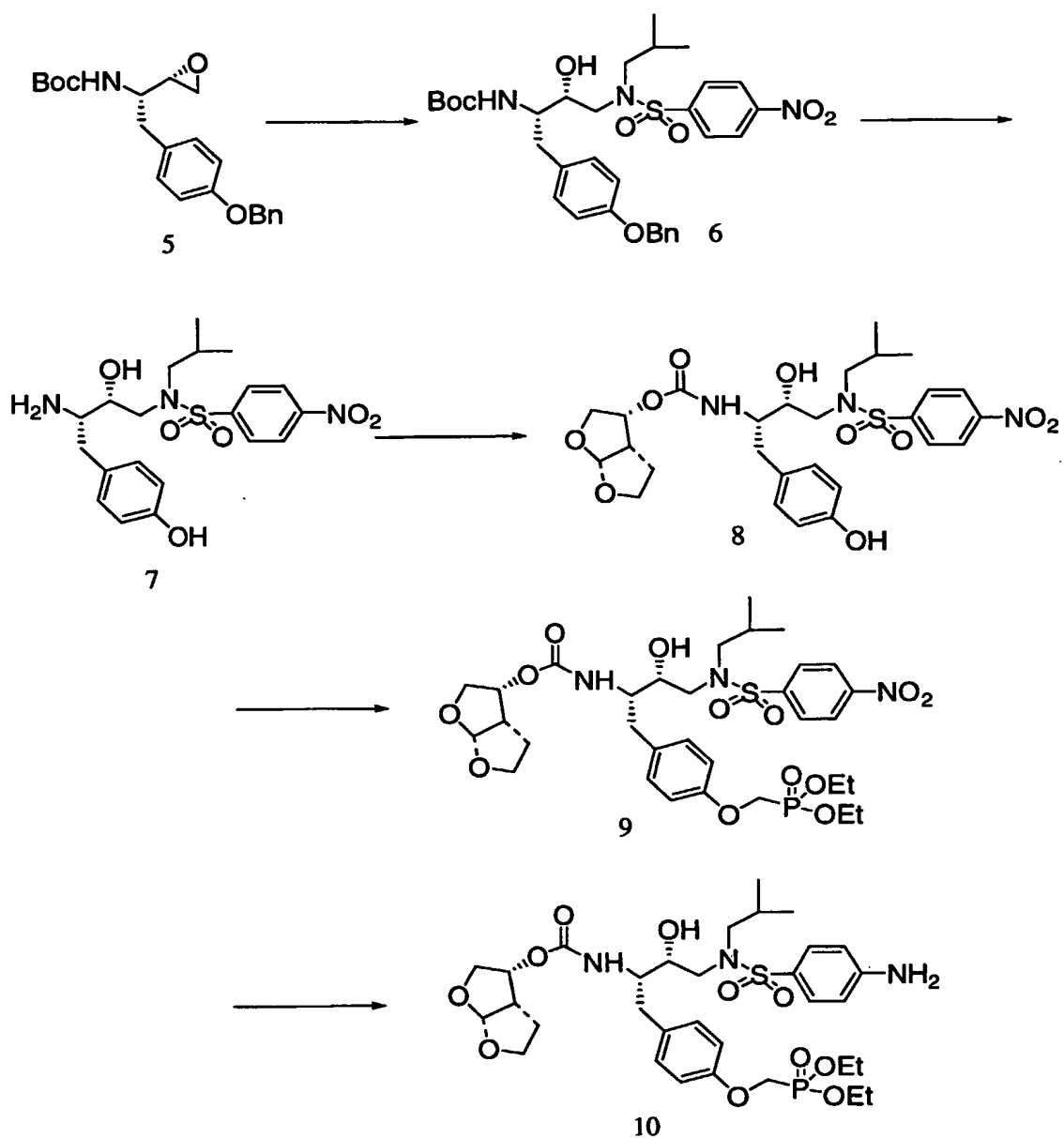
Scheme 4

Synthesis of Bisamidates

11

16 a,b,j and k
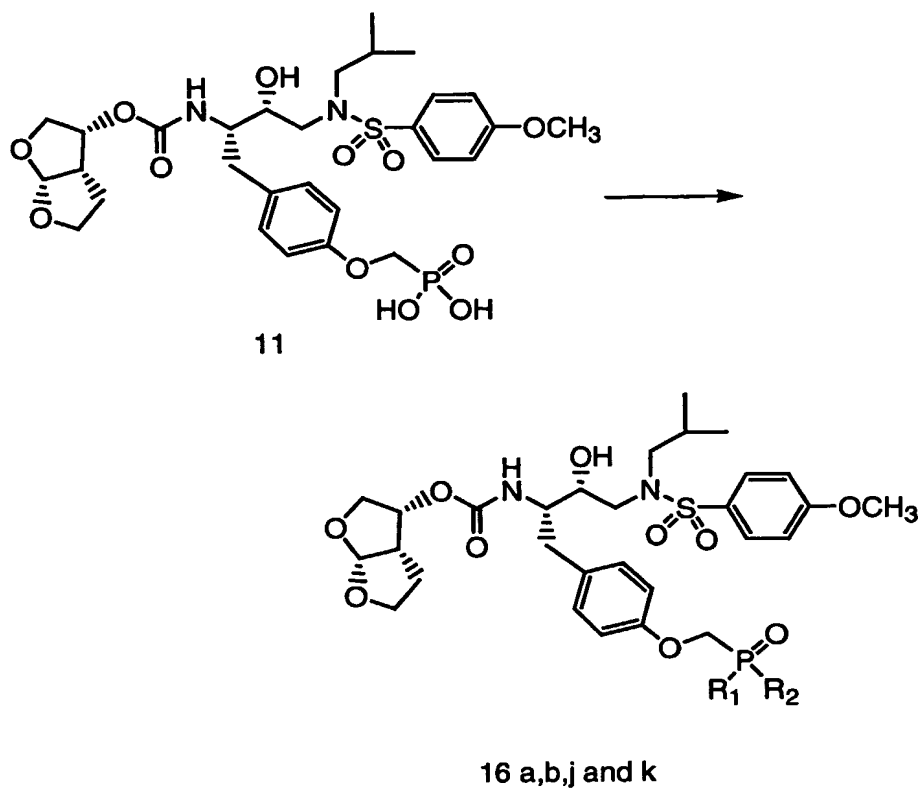
5

Compound	R₁	R₂
16a	Gly-Et	Gly-Et
16b	Gly-Bu	Gly-Bu
16j	Phe-Bu	Phe-Bu
16k	NHEt	NHEt

Scheme 5

Synthesis of Monoamidates
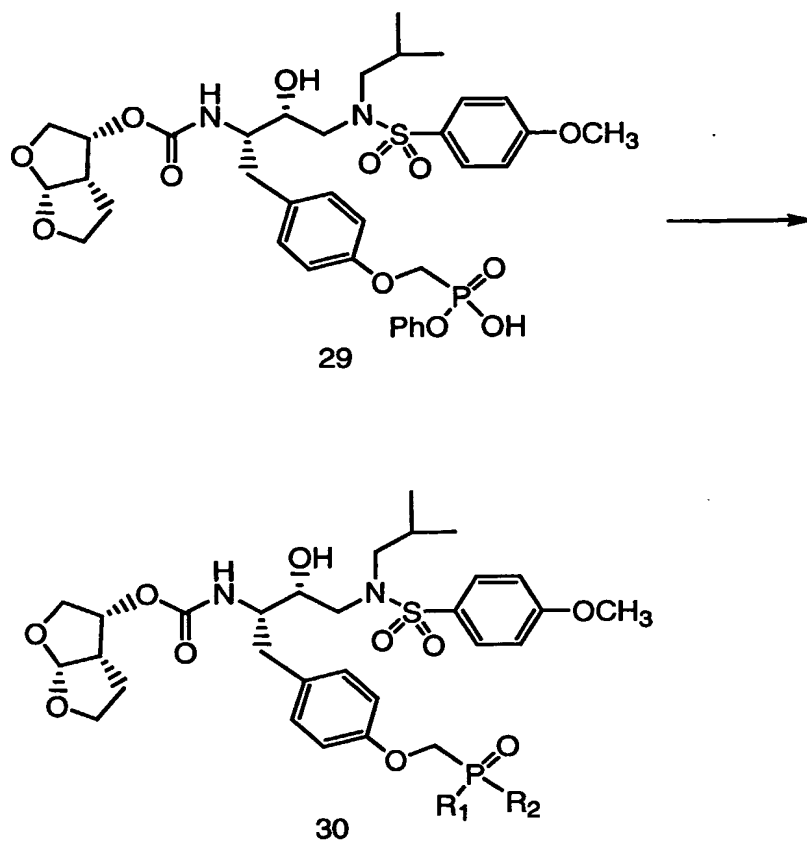
29

30

Compound	R₁	R₂
30a	OPh	Ala-Me
30b	OPh	Ala-Et
30c	OPh	(D)-Ala-iPr
30d	OPh	Ala-Bu
30e	OBn	Ala-Et

5

Scheme 6

OCH₃

2

OCH₃

R₁

R₂

30e
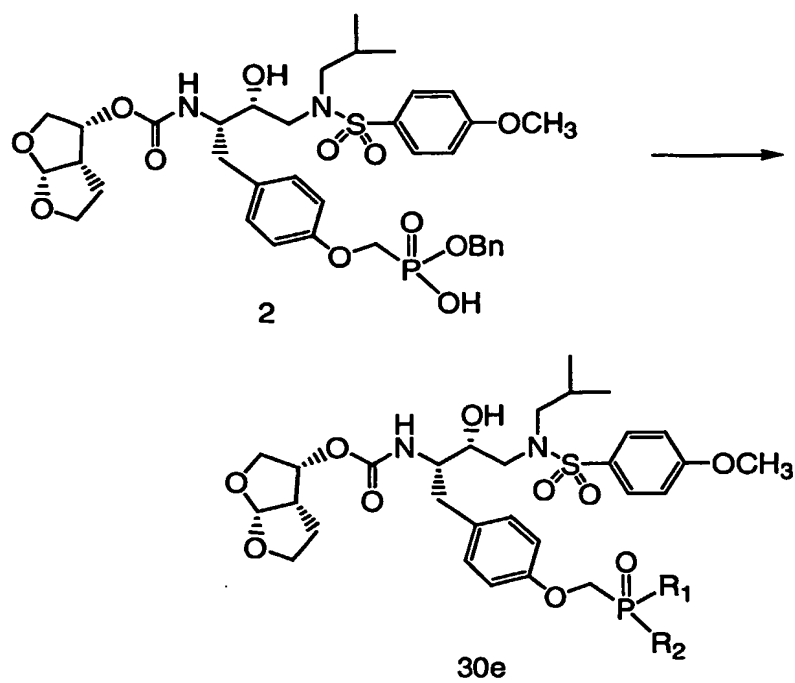
Scheme 7

Synthesis of Lactates
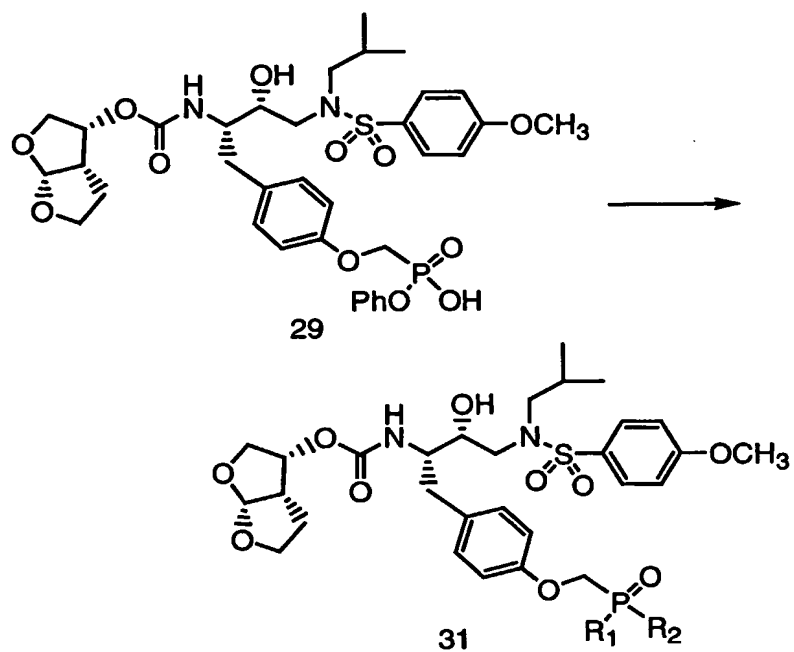
Compound	R₁	R₂
31a	OPh	Lac-iPr
31b	OPh	Lac-Et
31c	OPh	Lac-Bu
31d	OPh	(R)-Lac-Me
31e	OPh	(R)-Lac-Et

Scheme 8

5
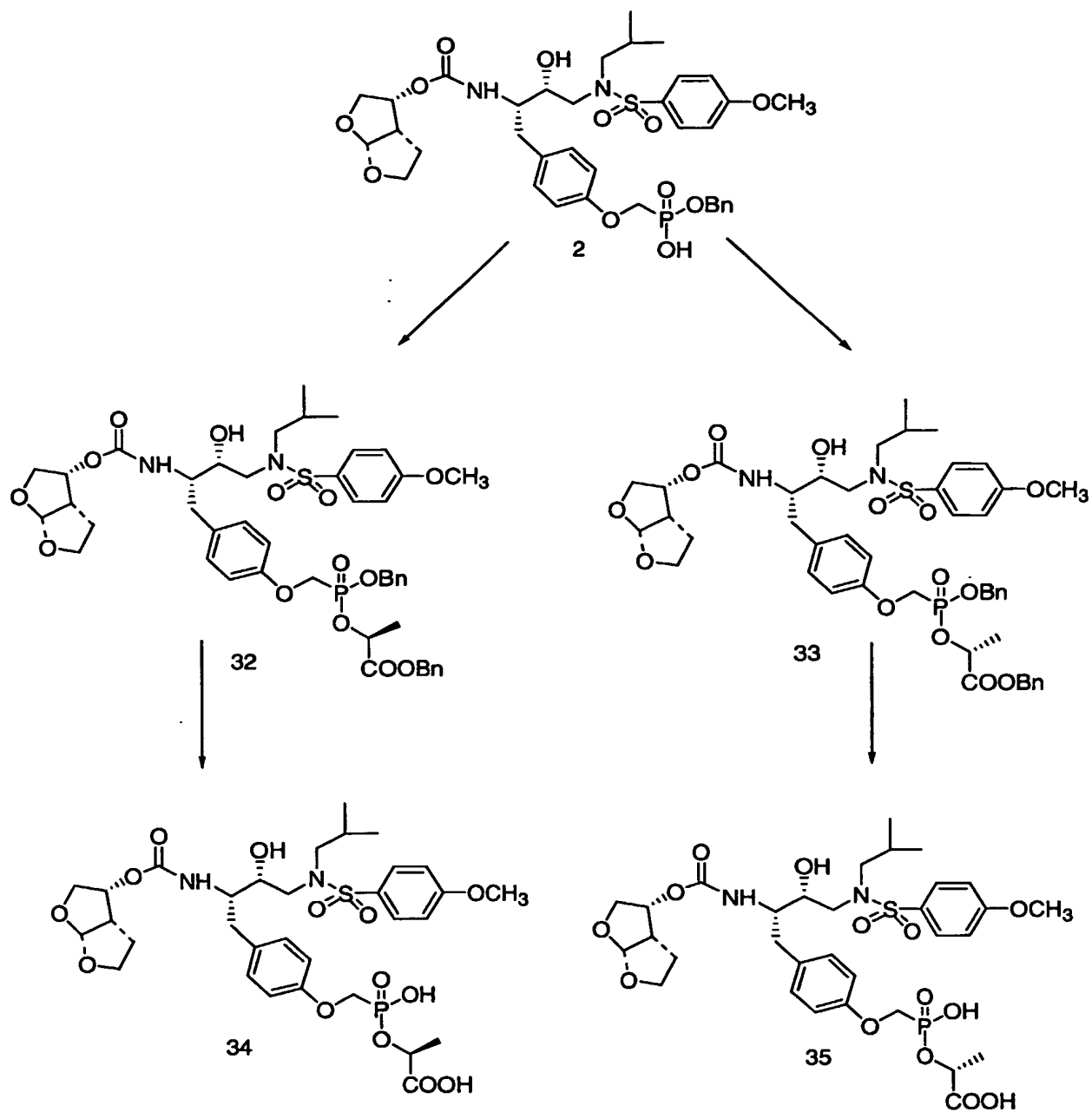
Scheme 9

Synthesis of Bislactate

11

36

5
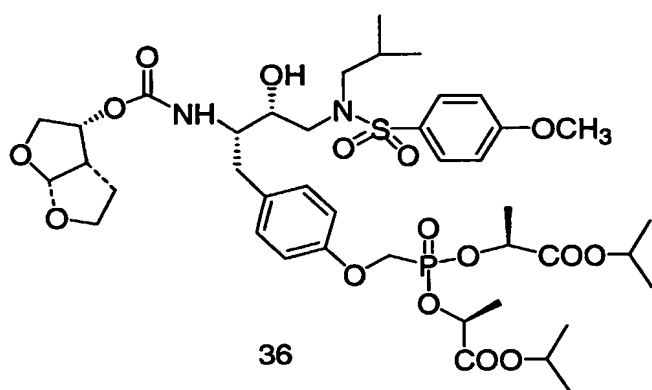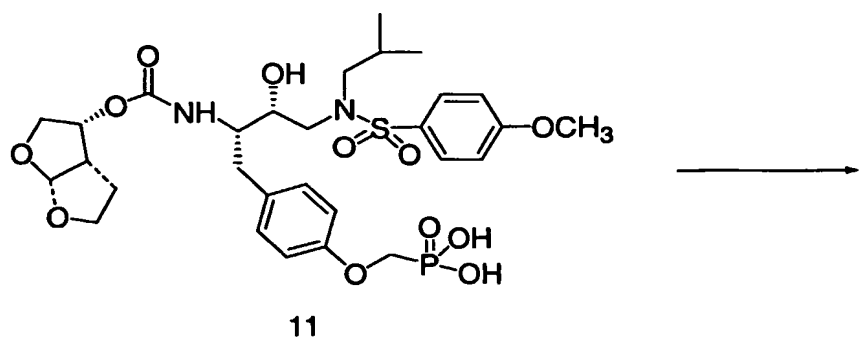
Examples

The following Examples refer to the Schemes.

5   Some Examples have been performed multiple times. In repeated Examples, reaction
     conditions such as time, temperature, concentration and the like, and yields were within
     normal experimental ranges. In repeated Examples where significant modifications were
     made, these have been noted where the results varied significantly from those described. In
     Examples where different starting materials were used, these are noted. When the repeated

10   Examples refer to a "corresponding" analog of a compound, such as a "corresponding ethyl
     ester", this intends that an otherwise present group, in this case typically a methyl ester, is
     taken to be the same group modified as indicated.

Example Section A

15   ## Example 1

     Diazo ketone 1: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-tyrosine (11 g, 30
     mmol, Fluka) in dry THF (55 mL) at -25-30°C (external bath temperature) was added
     isobutylchloroformate (3.9 mL, 30 mmol) followed by the slow addition of
     N.methylmorpholine (3.3 mL, 30 mmol). The mixture was stirred for 25 min, filtered while

20   cold, and the filter cake was rinsed with cold (0°C) THF (50 mL). The filtrate was cooled to
     - 25°C and diazomethane (~50 mmol, generated from 15 g Diazald according to Aldrichimica
     Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The
     reaction was stirred for 15 min and was then placed in an icebath at 0°C, allowing the bath to
     warm to room temperature while stirring overnight for 15 h. The solvent was evaporated

25   under reduced pressure and the residue was dissolved in EtOAc, washed with water, saturated
     NaHCO$_3$, saturated NaCl, dried (MgSO$_4$), filtered and evaporated to a pale yellow solid. The
     crude solid was slurried in hexane, filtered, and dried to afford the diazo ketone (10.9 g, 92%)
     which was used directly in the next step.

30   ## Example 2

     Chloroketone 2: To a suspension of diazoketone 1 (10.8 g, 27 mmol) in ether (600 mL) at
     0°C was added 4M HCl in dioxane (7.5 mL, 30 mmol). The solution was removed from the
     cooling bath, and allowed to warm to room temperature at which time the reaction was stirred
     1 h. The reaction solvent was evaporated under reduced pressure to give a solid residue that

was dissolved in ether and passed through a short column of silica gel. The solvent was evaporated to afford the chloroketone (10.7 g, 97%) as a solid.

Example 3

5   Chloroalcohol 3: To a solution of chloroketone 2 (10.6 g, 26 mmol) in THF (90 mL) was added water (10 mL) and the solution was cooled to 3-4°C (internal temperature). A solution of NaBH$_4$ (1.5 g, 39 mmol) in water (5 mL) was added dropwise over a period of 10 min. The mixture was stirred for 1h at 0°C and saturated KHSO$_4$ was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried

10   (MgSO$_4$) filtered and evaporated under reduced pressure. The crude product consisted of a 70:30 mixture of diastereomers by HPLC analysis (mobile phase, 77:25-CH$_3$CN:H$_2$O; flow rate: 1 mL/min; detection: 254 nm; sample volume: 20 μL; column: 5μ C18, 4.6X250 mm, Varian; retention times: major diastereomer 3, 5.4 min, minor diastereomer 4, 6.1 min). The residue was recrystallized from EtOAc/hexane twice to afford the chloro alcohol 3 (4.86g,

15   >99% diastereomeric purity by HPLC analysis) as a white solid.

Example 4

Epoxide 5: A solution of chloroalcohol 3 (4.32 g, 10.6 mmol) in EtOH (250 mL) and THF (100 mL) was treated with K$_2$CO$_3$ (4.4g, 325 mesh, 31.9 mmol) and the mixture was stirred

20   for at room temperature for 20h. The reaction mixture was filtered and was evaporated under reduced pressure. The residue was partitioned between EtOAc and water and the organic phase was washed with saturated NaCl, dried (MgSO$_4$), filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel to afford the epoxide (3.68 g, 94%) as a white solid.

25

Example 5

Sulfonamide 6: To a suspension of epoxide 5 (2.08 g, 5.6 mmol) in 2-propanol (20 mL) was added isobutylamine (10.7 mL, 108 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH$_2$Cl$_2$

30   (20 mL) and cooled to 0°C. N,N'-diisopropylethylamine (1.96 mL, 11.3 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (1.45 g, 7 mmol) in CH$_2$Cl$_2$ (5 mL) and the solution was stirred for 40 min at 0°C, warmed to room temperature and

evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaHCO$_3$. The organic phase was washed with saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide (2.79 g, 81%) as a small white needles: mp 122-

5   124°C (uncorrected).

Example 6

Carbamate 7: A solution of sulfonamide 6 (500 mg, 0.82 mmol) in CH$_2$Cl$_2$ (5 mL) at 0°C was treated with trifluoroacetic acid (5 mL). The solution was stirred at 0°C for 30 min and

10   was removed from the cold bath stirring for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between CH$_2$Cl$_2$ and saturated NaHCO$_3$. The aqueous phase was extracted twice with CH$_2$Cl$_2$ and the combined organic extracts were washed with saturated NaCl, dried (MgSO$_4$), filtered, and evaporated under reduced pressure. The residue was dissolved in CH$_3$CN (5 mL) and was treated with (3R,

15   3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (263 mg, 0.89 mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and N,N-dimethylaminopyridine (197 mg, 1.62 mmol). After stirring for 1.5h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 5% citric acid. The organic phase was washed twice with 1% K$_2$CO$_3$,

20   and then was washed with saturated NaCl, dried (MgSO$_4$), filtered, and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (1/1 - EtOAc/hexane) affording the carbamate (454 mg, 83%) as a solid: mp 128-129°C (MeOH, uncorrected).

25   Example 7

Phenol 8: A solution of carbamate 7 (1.15 g, 1.7 mmol) in EtOH (50 mL) and EtOAc (20 mL) was treated with 10% Pd/C (115 mg) and was stirred under H$_2$ atmosphere (balloon) for 18h. The reaction solution was purged with N$_2$, filtered through a 0.45 µM filter and was evaporated under reduced pressure to afford the phenol as a solid that contained residual

30   solvent: mp 131-134°C (EtOAc/hexane, uncorrected).

Example 8

Dibenzylphosphonate 10: To a solution of dibenzylhydroxymethyl phosphonate (527 mg,

1.8 mmol) in CH_2Cl_2 (5 mL) was treated with 2,6-lutidine (300 μL, 2.6 mmol) and the

reaction flask was cooled to -50°C (external temperature). Trifluoromethanesulfonic

anhydride (360 μL, 2.1 mmol) was added and the reaction mixture was stirred for 15 min and

5   then the cooling bath was allowed to warm to 0°C over 45 min. The reaction mixture was

partitioned between ether and ice-cold water. The organic phase was washed with cold 1M

H_3PO_4, saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure to

afford triflate 9 (697 mg, 91%) as an oil which was used directly without any further

purification. To a solution of phenol 8 (775 mg, 1.3 mmol) in THF (5 mL) was added

10   Cs_2CO_3 (423 mg, 1.3 mmol) and triflate 9 (710 mg, 1.7 mmol) in THF (2 mL). After stirring

the reaction mixture for 30 min at room temperature additional Cs_2CO_3 (423 mg, 1.3 mmol)

and triflate (178 mg, 0.33 mmol) were added and the mixture was stirred for 3.5h. The

reaction mixture was evaporated under reduced pressure and the residue was partitioned

between EtOAc and saturated NaCl. The organic phase was dried (MgSO$_4$), filtered and

15   evaporated under reduced pressure. The crude product was chromatographed on silica gel

eluting (5% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate as an oil that solidified

upon standing. The solid was dissolved in EtOAc, ether was added, and the solid was

precipitated at room temperature overnight. After cooling to 0°C, the solid was filtered and

washed with cold ether to afford the dibenzylphosphonate (836 mg, 76%) as a white solid:

20   ^{1}H NMR (CDCl$_3$) δ 7.66 (d, 2H), 7.31 (s, 10H), 7.08 (d, 2H), 6.94 (d, 2H), 6.76 (d, 2H), 5.59

(d, 1H), 5.15-4.89 (m, 6H), 4.15 (d, 2H), 3.94-3.62 (m, 10H), 3.13-2.69 (m, 7H), 1.78 (m,

1H), 1.70-1.44 (m, 2H), 0.89-0.82 (2d, 6H); ^{31}P NMR (CDCl$_3$) δ 18.7; MS (ESI) 853 (M+H).

Example 9

25   Phosphonic acid 11: A solution of dibenzylphosphonate 10 (0.81 g) was dissolved in EtOH/

EtOAc (30mL/10 mL), treated with 10% Pd/C (80 mg) and was stirred under H$_2$ atmosphere

(balloon) for 1.5h. The reaction was purged with N$_2$, and the catalyst was removed by

filtration through celite. The filtrate was evaporated under reduced pressure and the residue

was dissolved in MeOH and filtered with a 0.45 μM filter. After evaporation of the filtrate,

30   the residue was triturated with ether and the solid was collected by filtration to afford the

phosphonic acid (634 mg, 99%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.77 (d, 2H), 7.19 (d,

2H), 7.09 (d, 2H), 6.92 (d, 2H), 5.60 (d, 1H), 4.95 (m, 1H), 4.17 (d, 2H), 3.94 (m, 1H), 3.89

(s, 3H), 3.85-3.68 (m, 5H), 3.42 (dd, 1H), 3.16-3.06 (m, 2H), 2.96-2.84 (m, 3H), 2.50 (m, 1H), 2.02 (m, 1H), 1.58 (m, 1H), 1.40 (dd, 1H), 0.94 (d, 3H), 0.89 (d, 3H); ^{31}P NMR (CDCl$_3$) δ 16.2; MS (ESI) 671 (M-H).

5   Example 10

Diethylphosphonate 13: Triflate 12 was prepared from diethyl hydroxymethylphosphonate (2g, 11.9 mmol), 2,6-lutidine (2.1 mL, 17.9 mmol), and trifluoromethanesulfonic anhydride (2.5 mL, 14.9 mmol) as described for compound 9. To a solution of phenol 8 (60 mg, 0.10 mmol) in THF (2 mL) was added Cs$_2$CO$_3$ (65mg, 0.20 mmol) and triflate 12 (45 mg, 0.15

10   mmol) in THF (0.25 mL). The mixture was stirred at room temperature for 2h and additional triflate (0.15 mmol) in THF (0.25 mL) was added. After 2h the reaction mixture was partitioned between EtOAc and saturated NaCl. The organic phase was dried (MgSO$_4$), filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (EtOAc) to give a residue that was purified by chromatography on silica gel (5% 2-

15   propanol /CH$_2$Cl$_2$) to afford the diethylphosphonate as a foam: ^{1}H NMR (CDCl$_3$) δ 7.66 (d, 2H), 7.10 (d, 2H), 6.94 (d, 2H), 6.82 (d, 2H), 5.60 (d, 1H), 4.97 (d, 2H), 4.23-4.13 (m, 6H), 3.93-3.62 (m, 10H), 3.12-2.68 (m, 7H), 1.84-1.44 (m, 3H), 1.31 (t, 6H), 0.88-0.82 (2d, 6H); ^{31}P NMR (CDCl$_3$) δ 17.7; MS (ESI) 729 (M+H).

20   Example 11

Diphenylphosphonate 14: To a solution of 11 (100mg, 0.15 mmol) and phenol (141 mg, 1.5 mmol) in pyridine (1.5 mL) was added N, N-diisopropylcarbodiimide (50 μL, 0.38 mmol). The solution was stirred for 31h at room temperature and for 20h at 50°C. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel eluting

25   (EtOAc) to provide diphenylphosphonate 14 (16 mg) as a foam: ^{31}P NMR (CDCl$_3$) δ 10.9; MS (ESI) 847 (M+Na).

Example 12

Bis-Poc-phosphonate 15: To a solution of 11 (50 mg, 0.74 mmol) and isopropylchloromethyl

30   carbonate (29 mg, 0.19 mmol) in DMF (0.5 mL) was added triethylamine (26 μL, 0.19 mmol) and the solution was heated at 70°C (bath temperature) for 4.5h. The reaction was concentrated under reduced pressure and the residue was purified by preparative layer

chromatography (2% 2-propanol/ CH$_2$Cl$_2$) to afford 15 (7 mg): ^{1}H NMR (CDCl$_3$) δ 7.71 (d, 2H), 7.15 (d, 2H); 7.01 (d, 2H), 6.93 (d, 2H), 5.80-5.71 (m, 4H), 5.67 (d, 1H), 5.07-4.87 (m, 4H), 4.35 (d, 2H), 4.04-3.68 (m, 10H), 3.13 (dd, 1H), 3.04-2.90 (m, 5H), 2.79 (dd, 1H), 1.88-1.50 (m, 3H+H$_2$O peak), 1.30 (m, 12H), 0.93 (d, 3H), 0.88 (d, 3H); ^{31}P NMR (CDCl$_3$) δ 19.6.

5

Example 13

Synthesis of Bisamidates 16a-j. Representative Procedure, Bisamidate 16f: A solution of phosphonic acid 11 (100 mg, 0.15 mmol) and (S)-2-aminobutyric acid butyl ester hydrochloride (116 mg, 0.59 mmol) was dissolved in pyridine (5 mL) and the solvent was

10   distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph$_3$P (117 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (98 mg, 0.45 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH$_2$Cl$_2$). The purified product was suspended in ether and was evaporated under reduced pressure to afford

15   bisamidate 16f (106 mg, 75%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.72 (d, 2H), 7.15 (d, 2H), 7.01 (d, 2H), 6.87 (d, 2H), 5.67 (d, 1H), 5.05 (m, 1H), 4.96 (d, 1H), 4.19-3.71 (m overlapping s, 18H,), 3.42 (t, 1H), 3.30 (t, 1H), 3.20 (dd, 1H), 3.20-2.97 (m, 4H), 2.80 (dd, 2H), 1.87-1.54 (m, 19H), 1.42-1.35 (4H), 0.97-0.88 (m, 18H); ^{31}P NMR (CDCl$_3$) δ 20.3; MS (ESI) 955 (M+H).

20

Compound	R$_1$	R$_2$	Amino Acid
16a	H	Et	Gly
16b	H	Bu	Gly
16c	Me	Et	Ala
16d	Me	Bu	Ala
16e	Et	Et	Aba^1
16f	Et	Bu	Aba^1
16g	iBu	Et	Leu
16h	iBu	Bu	Leu
16i	Bn	Et	Phe
16j	Bn	Bu	Phe

^{1} Aba, 2-aminobutyric acid

Example 14
Diazo ketone 17: To a solution of N-tert-Butoxycarbonyl-p-bromo-L-phenylalanine (9.9 g,

25   28.8 mmol, Synthetech) in dry THF (55 mL) at -25-30°C (external bath temperature) was added isobutylchloroformate (3.74 mL, 28.8 mmol) followed by the slow addition of N-

methylmorpholine (3.16 mL, 28.8 mmol). The mixture was stirred for 25 min, filtered while cold, and the filter cake was rinsed with cold (0°C) THF (50 mL). The filtrate was cooled to - 25°C and diazomethane (~50 mmol, generated from 15 g diazald according to Aldrichimica Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min and was then placed in an icebath at 0°C, allowing the bath to warm to room temperature while stirring overnight for 15 h. The solvent was evaporated under reduced pressure and the residue was suspended in ether, washed with water, saturated NaHCO₃, saturated NaCl, dried (MgSO₄), filtered and evaporated to a pale yellow solid. The crude solid was slurried in hexane, filtered, and dried to afford diazo ketone 17 (9.73 g, 90%) which was used directly in the next step.

Example 15

Chloroketone 18: To a solution of diazoketone 17 (9.73 g, 26 mmol) in ether (500 mL) at 0°C was added 4M HCl in dioxane (6.6 mL, 26 mmol). The solution was stirred for 1 h at 0°C and 4M HCl in dioxane (1 mL) was added. After 1h, the reaction solvent was evaporated under reduced pressure to afford the chloroketone 18 (9.79 g, 98%) as a white solid.

Example 16

Chloroalcohol 19: A solution of chloroketone 18 (9.79g, 26 mmol) in THF (180 mL) and water (16 mL) was cooled to 0°C (internal temperature). Solid NaBH₄ (2.5 g, 66 mmol) was added in several portions over a period of 15 min while maintaining the internal temperature below 5°C. The mixture was stirred for 45 min and saturated KHSO₄ was slowly added until the pH<3. The mixture was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with brine, dried (MgSO₄) filtered and evaporated under reduced pressure. The residue was dissolved in EtOAc, and was passed through a short column of silica gel, and the solvent was evaporated. The solid residue was recrystallized from EtOAc/hexane to afford the chloroalcohol 19 (3.84g) as a white solid.

Example 17

Epoxide 21: A partial suspension of chloroalcohol 19 (1.16g, 3.1 mmol) in EtOH (50 mL) was treated with K₂CO₃ (2g, 14.5 mmol) and the mixture was stirred for 4 h at room

temperature. The reaction mixture was diluted with EtOAc, filtered, and the solvents were evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl, and the organic phase was dried (MgSO$_4$), filtered, and evaporated under reduced pressure to afford epoxide 21 (1.05g, 92%) as a white crystalline solid.

5

Example 18

Sulfonamide 22: To a solution of epoxide 21 (1.05g, 3.1 mmol) in 2-propanol (40 mL) was added isobutylamine (6 mL, 61 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH$_2$Cl$_2$

10 (20 mL) and cooled to 0°C. Triethylamine (642 µL, 4.6 mmol) was added followed by the addition of (634 mg, 3.4 mmol) in CH$_2$Cl$_2$ (5 mL) and the solution was stirred for 2h at 0°C at which time the reaction solution was treated with additional triethylamine (1.5 mmol) and 4-methoxybenzenesulfonyl chloride (0.31 mmol). After 1.5 h, the reaction solution was evaporated under reduced pressure. The residue was partitioned between EtOAc and cold

15 1M H$_3$PO$_4$. The organic phase was washed with saturated NaHCO$_3$, saturated NaCl, dried (MgSO$_4$), filtered and the solvent was evaporated under reduced pressure. The crude product was purified on silica gel (15/1 - CH$_2$Cl$_2$/EtOAc) to afford 1.67g of a solid which was recrystallized from EtOAc/hexane to give sulfonamide 22 (1.54g, 86%) as a white crystalline solid.

20

Example 19

Silyl ether 23: To a solution of the sulfonamide 22 (1.53g, 2.6 mmol) in CH$_2$Cl$_2$ (12 mL) at 0°C was added N,N-diisopropylethylamine (0.68 mL, 3.9 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (0.75 mL, 3.3 mmol). The reaction solution

25 was stirred for 1 h at 0°C and was warmed to room temperature, stirring for 17 h. Additional N,N-diisopropylethylamine (3.9 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (1.6 mmol) was added, stirred for 2.5h, then heated to reflux for 3h and stirred at room temperature for 12 h. The reaction mixture was partitioned between EtOAc and cold 1M H$_3$PO$_4$. The organic phase was washed with saturated NaHCO$_3$, saturated NaCl, and was

30 dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product was purified on silica gel (2/1 - hexane/ether) to afford silyl ether 23 (780 mg, 43%) as an oil.

Example 20

Phosphonate 24: A solution of 23 (260 mg, 0.37 mmol), triethylamine (0.52 mL, 3.7 mmol), and diethylphosphite (0.24 mmol, 1.85 mmol) in toluene (2 mL) was purged with argon and to the solution was added $(Ph_3P)_4Pd$ (43 mg, 10 mol%). The reaction mixture was heated at 110°C (bath temperature) for 6 h, and was then allowed to stir at room temperature for 12h.

5   The solvent was evaporated under reduced pressure and the residue was partitioned between ether and water. The aqueous phase was extracted with ether and the combined organic extracts were washed with saturated NaCl, dried ($MgSO_4$), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (2/1 - ethyl acetate/hexane) to afford diethylphosphonate 24 (153 mg, 55%).

10

Example 21

Phosphonic acid 26: To a solution of 24 (143 mg) in MeOH (5 mL) was added 4N HCl (2 mL). The solution was stirred at room temperature for 9h and was evaporated under reduced pressure. The residue was triturated with ether and the solid was collected by filtration to

15   provide hydrochloride salt 25 (100 mg, 92%) as a white powder. To a solution of X (47 mg, 0.87 mmol) in CH_3CN (1 mL) at 0°C was added TMSBr (130 μL, 0.97 mmol). The reaction was warmed to room temperature and stirred for 6.5h at which time TMSBr (0.87 mmol) was added and stirring was continued for 16h. The solution was cooled to 0°C and was quenched with several drops of ice-cold water. The solvents were evaporated under reduced pressure

20   and the residue was dissolved in several milliliters of MeOH and treated with propylene oxide (2 mL). The mixture was heated to gentle boiling and evaporated. The residue was triturated with acetone and the solid was collected by filtration to give phosphonic acid 26 (32 mg, 76%) as a white solid.

25   Example 22

Phosphonate 27: To a suspension of 26 (32 mg, 0.66 mmol) in CH_3CN (1 mL) was added bis(trimethylsilyl)acetamide (100 μL, 0.40 mmol) and the solution was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in CH_3CN (1 mL). To this solution was added (3R, 3aR, 6aS)-hexahydrofuro[2, 3-

30   b]furan-2-yl 4-nitrophenyl carbonate (20 mg, 0.069 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.), N,N-diisopropylethylamine (35 μL, 0.20 mmol), and N,N-dimethylaminopyridine (catalytic amount). The solution was stirred for 22h at room temperature, diluted with water (0.5 mL) and was stirred with IR 120 ion exchange resin (325

mg, H^{+} form) until the pH was <2. The resin was removed by filtration, washed with methanol and the filtrate was concentrated under reduced pressure. The residue was dissolved water, treated with solid NaHCO$_3$ until pH=8 and was evaporated to dryness. The residue was dissolved in water and was purified on C18 reverse phase chromatography eluting with water followed by 5%, 10% and 20% MeOH in water to give the disodium salt 27 (24 mg) as a pale yellow solid: ^{1}H NMR (D$_2$O) δ 7.72 (d, 2H), 7.52 (dd, 2H), 7.13 (dd, 2H), 7.05 (d, 2H), 5.58 (d, 1H), 4.87 (m, 1H), 3.86-3.53 (m overlapping s, 10H), 3.22 (dd, 1H), 3.12-2.85 (6H), 2.44 (m, 1H), 1.83 (m, 1H), 1.61 (m, 1H)1.12 (dd, 1H), 0.77 (m, 6H); ^{31}P NMR (D$_2$O) δ 11.23 ; MS (ESI) 641 (M-H).

Example 23

Diethylphosphonate 28: To a solution of 25 (16 mg, 0.028 mmol) in CH$_3$CN (0.5 mL) was added (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (9 mg, 0.031 mmol), N,N-diisopropylethylamine (20 μL, 0.11 mmol), and N,N-dimethylaminopyridine (catalytic amount). The solution was stirred at room temperature for 48 h and was then concentrated under reduced pressure. The residue was partitioned between EtOAc and saturated NaHCO$_3$. The organic phase was washed with saturated NaHCO$_3$, saturated NaCl, and was dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (2.5-5% 2-propanol/CH$_2$Cl$_2$). The residue obtained was further purified by preparative layer chromatography (5% MeOH/CH$_2$Cl$_2$) followed by column chromatography on silica gel (10% 2-propanol/CH$_2$Cl$_2$) to afford diethylphosphonate 28 (7 mg) as a foam: ^{1}H NMR (CDCl$_3$) δ 7.72-7.66 (m, 4H), 7.32-7.28 (2H), 6.96 (d, 2H), 5.60 (d, 1H), 4.97 (m, 2H), 4.18-4.01 (m, 4H), 3.94-3.60 (m overlapping s, 10H), 3.15-2.72 (m, 7H), 1.78 (m, 1H), 1.61 (m+H$_2$O, ~3H), 1.28 (t; 6H), 0.86 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 18.6 ; MS (ESI) 699 (M+H).

Prospective Example 24

Diphenyl phosphonate 14 is treated with aqueous sodium hydroxide to provide monophenyl phosphonate 29 according to the method found in J. Med. Chem. 1994, 37, 1857.

Monophenyl phosphonate 29 is then converted to the monoamidate 30 by reaction with an amino acid ester in the presence of Ph$_3$ and 2,2'-dipyridyl disulfide as described in the synthesis of bisamidate 16f. Alteratively, monoamidate 30 is prepared by treating 29 with an

amino acid ester and DCC. Coupling conditions of this type are found in Bull. Chem. Soc. Jpn. 1988, 61, 4491.

Example 25

Diazo ketone 1: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-tyrosine (25 g, 67 mmol, Fluka) in dry THF (150 mL) at -25-30°C (external bath temperature) was added isobutylchloroformate (8.9 mL, 69 mmol) followed by the slow addition of N.methylmorpholine (37.5 mL, 69 mmol). The mixture was stirred for 40 min, and diazomethane (170 mmol, generated from 25 g 1-methyl-3-nitro-1-nitroso-guanidine according to Aldrichimica Acta 1983, 16, 3) in ether (400 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min allowing the bath to warm to room temperature while stirring overnight for 4 h. The mixture was bubbled with N2 for 30 min., washed with water, saturated NaHCO3, saturated NaCl, dried (MgSO4), filtered and evaporated to a pale yellow solid. The crude solid was slurried in hexane, filtered, and dried to afford the diazo ketone (26.8 g, 99%) which was used directly in the next step.

Example 26

Chloroketone 2: To a suspension of diazoketone 1 (26.8 g, 67 mmol) in ether/THF (750 mL, 3/2) at 0°C was added 4M HCl in dioxane (16.9 mL, 67 mmol). The solution was stirred at 0°C for 2 hr. The reaction solvent was evaporated under reduced pressure to give the chloroketone (27.7 g, 97%) as a solid.

Example 27

Chloroalcohol 3: To a solution of chloroketone 2 (127.1 g, 67 mmol) in THF (350 mL) was added water (40 mL) and the solution was cooled to 3-4°C (internal temperature). NaBH4 (6.3 g, 168 mmol) was added in portions. The mixture was stirred for 1h at 0°C and the solvents were removed. The mixture was diluted with ethyl acetate and saturated KHSO4 was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried (MgSO4) filtered and evaporated under reduced pressure. The crude product consisted of a 70:30 mixture of diastereomers by HPLC analysis (mobile phase, 77:25-CH3CN:H2O; flow rate: 1 mL/min; detection: 254 nm; sample volume: 20 µL; column: 5µ C18, 4.6X250 mm, Varian; retention times: major diastereomer 3, 5.4 min, minor

diastereomer 4, 6.1 min). The residue was recrystallized from EtOAc/hexane twice to afford the chloro alcohol 3 (12.2g, >96% diastereomeric purity by HPLC analysis) as a white solid.

Example 28

5   Epoxide 5: To a solution of chloroalcohol 3 (12.17 g, 130 mmol) in EtOH (300 mL) was added KOH/EtOH solution (0.71N, 51 mL, 36 mmol). The mixture was stirred for at room temperature for 1.5h. The reaction mixture was evaporated under reduced pressure. The residue was partitioned between EtOAc and water and the organic phase was washed with saturated NH4Cl, dried (MgSO4), filtered, and evaporated under reduced pressure to afford

10   the epoxide (10.8 g, 97%) as a white solid.

Example 29

Sulfonamide 6: To a suspension of epoxide 5 (10.8 g, 30 mmol) in 2-propanol (100 mL) was added isobutylamine (129.8 mL, 300 mmol) and the solution was refluxed for 1 hr. The

15   solution was evaporated under reduced pressure to give a crude solid. The solid (42 mmol) was dissolved in CH2Cl2 (200 mL) and cooled to 0°C. Triethylamine (11.7 mL, 84 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (8.68 g, 42 mmol) and the solution was stirred for 40 min at 0°C, warmed to room temperature and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaHCO3.

20   The organic phase was washed with saturated NaCl, dried (MgSO4), filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide (23.4 g, 91%) as a small white needles: mp 122-124°C (uncorrected).

Example 30

25   Carbamate 7: A solution of sulfonamide 6 (6.29 mg, 10.1 mmol) in CH2Cl2 (20 mL) was treated with trifluoroacetic acid (10 mL). The solution was stirred for 3 hr. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase were washed with 0.5 N NaOH (2x), water (2x) and saturated NaCl, dried (MgSO4), filtered, and evaporated under reduced pressure. The residue was

30   dissolved in CH3CN (60 mL), cooled to 0°C and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (298.5 g, 10 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.) and N,N-dimethylaminopyridine (2.4 g, 20 mmol). After stirring for 1h at 0°C, the reaction solvent was evaporated under

reduced pressure and the residue was partitioned between EtOAc and 5% citric acid.   The

organic phase was washed twice with 1% K₂CO₃, and then was washed with saturated NaCl,

dried (MgSO₄), filtered, and evaporated under reduced pressure. The crude product was

purified by chromatography on silica gel (1/1 - EtOAc/hexane) affording the carbamate (5.4

5   g, 83%) as a solid: mp 128-129°C (MeOH, uncorrected).

Example 31

Phenol 8: A solution of carbamate 7 (5.4 g, 8.0 mmol) in EtOH (260 mL) and EtOAc (130

mL) was treated with 10% Pd/C (540 mg) and was stirred under H₂ atmosphere (balloon) for

10   3h. The reaction solution stirred with celite for 10 min, and passed through a pad of celite.

The filtrate was evaporated under reduced pressure to afford the phenol as a solid (4.9 g) that

contained residual solvent: mp 131-134°C (EtOAc/hexane, uncorrected).

Example 32

15   Dibenzylphosphonate 10: To a solution of dibenzylhydroxymethyl phosphonate (3.1 g, 10.6

mmol) in CH₂Cl₂ (30 mL) was treated with 2,6-lutidine (1.8 mL, 15.6 mmol) and the reaction

flask was cooled to -50°C (external temperature). Trifluoromethanesulfonic anhydride (2.11

mL, 12.6 mmol) was added and the reaction mixture was stirred for 15 min and then the

cooling bath was allowed to warm to 0°C over 45 min. The reaction mixture was partitioned

20   between ether and ice-cold water. The organic phase was washed with cold 1M H₃PO₄,

saturated NaCl, dried (MgSO₄), filtered and evaporated under reduced pressure to afford

triflate 9 (3.6 g, 80%) as an oil which was used directly without any further purification. To a

solution of phenol 8 (3.61 g, 6.3 mmol) in THF (90 mL) was added Cs₂CO₃ (4.1 g, 12.6

mmol) and triflate 9 (4.1 g, 9.5 mmol) in THF (10 mL). After stirring the reaction mixture

25   for 30 min at room temperature additional Cs₂CO₃ (6.96 g, 3 mmol) and triflate (1.26 g, 3

mmol) were added and the mixture was stirred for 3.5h. The reaction mixture was

evaporated under reduced pressure and the residue was partitioned between EtOAc and

saturated NaCl. The organic phase was dried (MgSO₄), filtered and evaporated under

reduced pressure. The crude product was chromatographed on silica gel eluting (5% 2-

30   propanol/CH₂Cl₂) to give the dibenzylphosphonate as an oil that solidified upon standing.

The solid was dissolved in EtOAc, ether was added, and the solid was precipitated at room

temperature overnight. After cooling to 0°C the solid was filtered and washed with cold ether

to afford the dibenzylphosphonate (3.43 g, 64%) as a white solid: ¹H NMR (CDCl₃) δ 7.66

(d, 2H), 7.31 (s, 10H), 7.08 (d, 2H), 6.94 (d, 2H), 6.76 (d, 2H), 5.59 (d, 1H), 5.15-4.89 (m, 6H), 4.15 (d, 2H), 3.94-3.62 (m, 10H), 3.13-2.69 (m, 7H), 1.78 (m, 1H), 1.70-1.44 (m, 2H), 0.89-0.82 (2d, 6H); ^{31}P NMR (CDCl$_3$) δ 18.7; MS (ESI) 853 (M+H).

5   Example 33

Phosphonic acid 11: A solution of dibenzylphosphonate 10 (3.43 g) was dissolved in EtOH/ EtOAc (150 mL/50 mL), treated with 10% Pd/C (350 mg) and was stirred under H$_2$ atmosphere (balloon) for 3 h. The reaction mixture was stirred with celite, and the catalyst was removed by filtration through celite. The filtrate was evaporated under reduced pressure

10   and the residue was dissolved in MeOH and filtered with a 0.45 μM filter. After evaporation of the filtrate, the residue was triturated with ether and the solid was collected by filtration to afford the phosphonic acid (2.6 g, 94%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.77 (d, 2H), 7.19 (d, 2H), 7.09 (d, 2H), 6.92 (d, 2H), 5.60 (d, 1H), 4.95 (m, 1H), 4.17 (d, 2H), 3.94 (m, 1H), 3.89 (s, 3H), 3.85-3.68 (m, 5H), 3.42 (dd, 1H), 3.16-3.06 (m, 2H), 2.96-2.84 (m, 3H),

15   2.50 (m, 1H), 2.02 (m, 1H), 1.58 (m, 1H), 1.40 (dd, 1H), 0.94 (d, 3H), 0.89 (d, 3H); ^{31}P NMR (CDCl$_3$) δ 16.2; MS (ESI) 671 (M-H).

Example Section B

There is no Section B in this application.

Example Section C

Example 1

Diphenyl phosphonate **31**: To a solution of phosphonic acid **30** (11 g, 16.4 mmol) and phenol
(11 g, 117 mmol) in pyridine (100 mL) was added 1, 3-dicyclohexylcarbodiimide (13.5 g,
65.5 mmol). The solution was stirred at room temperature for 5 min and then at 70°C for 2h.
The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100 mL)
and filtered. The filtrate was evaporated under reduced pressure to remove pyridine. The
residue was dissolved in ethyl acetate (250 mL) and acidified to pH = 4 by addition of HCl
(0.5 N) at 0°C. The mixture was stirred at 0°C for 0.5 h, filtered and the organic phase was
separated and washed with brine, dried over MgSO4, filtered and concentrated under reduced
pressure. The residue was purified on silica gel to give diphenyl phosphonate **31** (9 g, 67%)
as a solid. ^{31}P NMR (CDCl3) d 12.5.

Example 2

Monophenyl phosphonate **32**: To a solution of diphenylphosphonate **31** (9.0 g, 10.9 mmol) in
acetonitrile (400 mL) was added NaOH (1N, 27 mL) at 0°C. The reaction mixture was stirred at
0°C for 1 h, and then treated with Dowex (50WX8-200, 12 g). The mixture was stirred for 0.5 h
at 0°C, and then filtered. The filtrate was concentrated under reduced pressure and co-
evaporated with toluene. The residue was dissolved in ethyl acetate and hexane was added to
precipitate out the monophenyl phosphonate **32** (8.1 g, 100%). ^{31}P NMR (CDCl3) d 18.3.

Example 3

Monoamidate **33a** (R_1 = Me, R_2 = n-Bu): To a flask charged with monophenyl phosphonate
32 (4.0 g, 5.35 mmol) , was added L-alanine n-butyl ester hydrochloride (4.0 g, 22 mmol), 1,
3-dicyclohexylcarbodiimide (6.6 g, 32 mmol), and finally pyridine (30 mL) under nitrogen.
The resultant mixture was stirred at 60 – 70°C for 1 h, then cooled to room temperature and
diluted with ethyl acetate. The mixture was filtered and the filtrate was concentrated under
reduced pressure. The residue was partitioned between ethyl acetate and HCl (0.2 N) and the
organic layer was separated. The ethyl acetate phase was washed with water, saturated
NaHCO3, dried over MgSO4 , filtered and concentrated under reduced pressure. The residue
was purified on silica gel (pre-treated with 10% MeOH / CH3CO2Et, eluting with 40%
CH2Cl2 / CH3CO2Et and CH3CO2Et) to give two isomers of **33a** in a total yield of 51%.

Isomer A (1.1 g): 1H NMR (CDCl3) d 0.88 (m, 9H), 1.3 (m, 2H), 1.35 (d, J = 7 Hz, 3H), 1.55 (m, 2H), 1.55-1.7 (m, 2H), 1.8 (m, 1H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 9H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR (CDCl3) d

5   20.5. Isomer B (1.3 g) 1H NMR (CDCl3) d 0.88 (m, 9H), 1.3 (m, 2H), 1.35 (d, J = 7 Hz, 3H), 1.55 (m, 2H), 1.55-1.7 (m, 2H), 1.8 (m, 1H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 9H), 3.85 (s, 3H), 4.2-4.35 (m, 3H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR (CDCl3) d 19.4.

10   Example 4

Monoamidate **33b** (R$_1$ = Me, R$_2$ = i-Pr) was synthesized in the same manner as **33a** in 77% yield. Isomer A : 1H NMR (CDCl3) d 0.9 (2d, J = 6.3Hz, 6H), 1.2 (d, J = 7 Hz, 6H), 1.38 (d, J = 7 Hz, 3H), 1.55-1.9 (m, 3H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 8H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d,

15   J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR (CDCl3) d 20.4. Isomer B: 1H NMR (CDCl3) d 0.9 (2d, J = 6.3Hz, 6H), 1.2 (d, J = 7 Hz, 6H), 1.38 (d, J = 7 Hz, 3H), 1.55-1.9 (m, 3H), 2.7-3.2 (m, 7H), 3.65-4.1 (m, 8H), 3.85 (s, 3H), 4.2 (m, 1H), 4.3 (d, J = 9.6 Hz, 2H), 5.0 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 6.85 (d, J = 8.7 Hz, 2H), 7.0 (d, J = 8.7 Hz, 2H), 7.1-7.3 (m, 7H), 7.7 (d, J = 8.7 Hz, 2H); ^{31}P NMR (CDCl3) d 19.5.

Example Section D

Example 1
Cyclic Anhydride 1 (6.57 g, 51.3 mmol) was treated according to the procedure of Brown et
al., J. Amer. Chem. Soc. 1955, 77, 1089 -1091 to afford amino alcohol 3 (2.00g, 33%). *for
intermediate 2* : ^{1}H NMR (CD$_3$OD) δ 2.40 (S, 2H), 1.20 (s, 6H).

Example 2
Amino alcohol 3 (2.0 g, 17 mmol) was stirred in 30 mL 1:1 THF: water. Sodium
Bicarbonate (7.2 g, 86 mmol) was added, followed by Boc Anhydride (4.1 g, 19 mmol). The
reaction was stirred for 1 hour, at which time TLC in 5% methanol/DCM with ninhydrin stain
showed completion. The reaction was partitioned between water and ethyl acetate. The
organic layer was dried and concentrated, and the resulting mixture was chromatographed on
silica in 1:1 hexane: ethyl acetate to afford two fractions, "upper" and "lower" each having
the correct mass. By NMR the correct product 4 was "lower" (0.56 g, 14%) ^{1}H NMR
(CDCl$_3$) δ 3.7 (t, 2H), 3.0 (d,2H), 1.45 (t, 2H) 1.4 (s, 9H), 0.85 (s, 6H),
MS (ESI): 240 (M + 23).

Example 3
Sodium Hydride (60% emulsion in oil) was added to a solution of the alcohol 4
(1.1g, 5.2 mmol) in dry DMF in a 3-neck flask under dry nitrogen. Shortly afterward triflate
35 (2.4 g, 5.7 mmol) was added with stirring for 1.5 hrs. Mass spectrometry showed the
presence of the starting material (240, M+23), thus 100 mg more 60% sodium hydride
emulsion as well as ~1 g more triflate were added with an additional hour of stirring. The
reaction was quenched by the addition of saturated NaHCO$_3$ then partitioned between ethyl
acetate and water. The organic layer was dried with brine and MgSO$_4$ and eluted on silica
with 1:1 hexane:ethyl acetate to afford 5 (0.445 g, 15%). NMR showed some contamination
with alcohol 4 starting material. ^{1}H NMR (CDCl$_3$): δ 7.28 (s, 10H), 5.00 (m, 4H), 3.70 (t,
2H), 2.94, (d, 2H), 1.44 (t, 2H), 1.40 (s, 9H), 0.83 (s, 6H) MS (ESI): 514 (M+23).

Example 4
Phosphonate ester 5 (0.445 g, 0.906 mmol) was stirred with with 20% TFA in DCM. (5 mL)
TLC showed completion in 1 hr time. The reaction was azeotroped with toluene then run on

a silica gel column with 10% methanol in DCM. Subsequently, the product was dissolved in ethyl acetate and shaken with saturated sodium bicarbonate: water (1:1), dried with brine and magnesium sulfate to afford the free amine 6 (30mg, 8.5%). ^{1}H NMR (CDCl$_3$): δ 7.30 (s, 10H), 5.00 (m, 4H), 3.67 (d, 2H), 3.47, (t, 2H), 2.4-2.6 (brs) 1.45 (t, 2H), 0.82 (s, 6H), MS (ESI): 393 (M+1).

Example 5

Amine 6 (30 mg, 0.08 mmol) and epoxide 7 (21 mg, 0.08 mmol) were dissolved in 2 mL IprOH and heated to reflux for 1 hr then monitored by TLC in 10% MeOH/DCM. Added ~20 mg more epoxide 7 and continued reflux for 1 hr. Cool to room temperature, dilute with ethyl acetate, shake with water and brine, dry with magnesium sulfate. Silica gel chromatography using first 5% then 10% MeOH in EtOAc yielded amine 8 (18 mg, 36%). ^{1}H NMR (CDCl$_3$): δ 7.30 (s, 10H), 7.20-7-14 (m, 5H), 5.25-4.91 (m, 4H), 3.83, (m, 1H), 3.71 (d, 2H) 3.64 (m, 1H), 3.54 (t, 2H), 3.02-2.61 (m, 5H), 2.65-2.36 (dd, 2H) (t, 2H), 1.30 (s, 9H) 0.93 (s, 9H) 0.83 (t, 2H) MS (ESI) 655 (M+1).

Example 6

Amine 8 (18 mg, 0.027 mmol) was dissolved in 1 mL DCM then acid chloride 9 (6 mg, 0.2 mmol) followed by triethylamine (0.004 mL, 0.029 mmol). The reaction was monitored by TLC. Upon completion the reaction was diluted with DCM shaken with 5% citric acid, saturated sodium bicarbonate, brine, and dried with MgSO$_4$. Purification on silica (1:1 Hexane:EtOAc) afforded sulfonamide 10 (10.5 mg, 46%). ^{1}H NMR (CDCl$_3$): δ 7.69 (d, 2H), 7.30 (s, 10H), 7.24-7-18 (m, 5H), 5.00 (m, 4H), 4.73, (d, 1H), 4.19 (s, 1H) 3.81 (m, 1H), 3.80 (s, 3H), 3.71 (d,2H), 3.57 (t, 2H), 3.11-2.95 (m, 5H) 2.75 (m,1H)1.25 (s, 1H), 0.90 (s, 6H) MS (ESI) 847 (M+Na$^+$).

Example 7

Sulfonamide 10 (10.5 mg, 0.013 mmol) was stirred at room temperature in 20% TFA/DCM. Once Boc deprotection was complete by TLC (1:1 Hexane:EtOAc) and MS, the reaction was azeotroped with toluene. The TFA salt of the amine was dissolved in acetonitrile (0.5 mg) and to this were added carbonate 11 (4.3 mg, 0.014 mmol) followed by DMAP (4.6 mg, 0.038 mg). Stir at room temp until TLC (1:1 Hexane:EtOAc) shows completion. Solvent was evaporated and the residue was redissolved in EtOAc then shaken

with saturated $NaHCO_3$. The organic layer was washed with water and brine, then dried with $MgSO_4$ Purification on silica with Hexane: EtOAc afforded compound 12 (7.1 mg, 50%). ^{1}H NMR ($CDCl_3$): δ 7.75 (d, 2H) 7.24-7.35 (15H) 6.98 (d, 2H), 5.62 (d, 1H) 5.04 (m, 4H) 4.98 (m, 1H) 4.03 (m, 1H), 3.85 (s, 3H), 3.61-3.91 (9H), 3.23-3.04 (5H) 2.85 (m, 1H), 2.74 (m,1H) 1.61 (d, 2H), 1.55 (m, 1H) 1.36 (m, 1H) 0.96 (d, 6H) MS (ESI): 903 (M+23).

Example 8

Compound 12 (6.1 mg, 0.007 mmol) was dissolved in 1 mL 3:1 EtOH:EtoAc. Palladium catalyst (10% on C, 1mg) was added and the mixture was purged three times to vacuum with 1 atmosphere hydrogen gas using a balloon. The reaction was stirred for 2 hrs, when MS and TLC showed completion. The reaction was filtered through Celite with EtOH washing and all solvent to was evaporated to afford final compound 13 (5mg, 100%). ^{1}H NMR (CD_3OD): δ 7.79 (d, 2H) 7.16-7.24 (5H) 7.09 (d, 2H) 5.58 (d, 1H) 4.92 (m, 1H) 3.97 (m, 1H), 3.92 (dd,1H) 3.89 (s, 3H) 3.66-3.78 (8H) 3.40 (d,1H), 3.37 (dd, 1H), 3.15 (m, 1H) 3.12 (dd,1H) 2.96 (d, 1H), 2.87 (m, 1H), 2.74 (m,1H) 2.53 (m, 1H) 1.70 (m, 2H), 1.53 (m, 1H) 1.32 (m, 1H) 1.04 (d, 6H) MS (ESI): 723 (M+23).

Example 9

Amino Alcohol 14 (2.67g, 25.9 mmol) was dissolved in THF with stirring and Boc Anhydride (6.78g, 31.1 mmol) was added. Heat and gas evolution ensued. TEA (3.97 mL, 28.5 mmol) was added and the reaction was stirred overnight. In the morning, the reaction was quenched by the addition of saturated $NaHCO_3$. The organic layer was separated out and shaken with water, dried with brine and $MgSO_4$ to afford 15 which was used without further purification. (100% yield) (some contamination): ^{1}H NMR ($CDCl_3$): δ 3.76 (t ,1H) 3.20, (d,2H), 2.97 (d, 2H), 1.44 (s, 9H), 0.85 (s, 6H).

Example 10

A solution of the alcohol 15 (500 mg, 2.45 mmol) in dry THF was cooled under dry N_2 with stirring. To this was added n-butyl lithium (1.29 mL, 2.71 mmol) as a solution in hexane in a manner similar to that described in Tetrahedron. 1995, 51 #35, 9737-9746. Triflate 35 (1.15 g, 2.71 mmol) was added neat with a tared syringe. The reaction was stirred for four hours, then quenched with saturated $NaHCO_3$. The mixture was then partitioned between water and EtOAc. The organic layer was dried with brine and $MgSO_4$, then chromatographed on silica

in 1:1 Hexane:EtOAc to afford phosphonate 16 (445mg, 38%) ^{1}H NMR (CDCl$_3$): δ 7.37 (m,

10H), 5.09 (m, 4H), 3.73-3.75 (m, 2H), 3.24 (s,2H), 3.02 (d, 2H), 1.43 (s, 9H), 0.86 (s, 6H).

Example 11

Phosphonate 16 (249 mg, 0.522 mmol) was stirred in 20% TFA/DCM for 1 hr. The reaction

was then azeotroped with toluene. The residue was re-dissolved in EtOAc, then shaken with

water: saturated NaHCO$_3$ (1:1). The organic layer was dried with brine and MgSO$_4$ and

solvent was removed to afford amine 17 (143 mg, 73%) ^{1}H NMR (CDCl$_3$): δ 7.30 (s, 10H),

5.05-4.99 (m, 4H), 3.73 (d, 2H), 3.23 (s, 2H), 2.46 (brs, 2H), 0.80 (s, 6H) ^{31}P NMR (CDCl$_3$):

δ 23.77 (s).

Example 12

Amine 17 (143 mg, 0.379 mmol) and epoxide 7 (95 mg, 0.360 mmol) were dissolved in 3 mL

IprOH and heated to 85°C for 1 hr. The reaction was cooled to room temperature overnight

then heated to 85°C for 1 hr more in the morning. The reaction was then diluted with EtOAc,

shaken with water, dried with brine MgSO$_4$ and concentrated. The residue was eluted on

silica in a gradient from 5% to 10% MeOH in DCM to afford compound 18 (33 mg, 14%).

Example 13

Mix compound 18 (33 mg, 0.051 mmol) and chlorosulfonyl compound 9 (11 mg, 0.054

mmol) in 2 mL DCM then add TEA (0.0075 mL, 0.054 mmol), stir for 5 hrs. TLC in 1:1

EtOAc: hexane shows reaction not complete. Place in freezer overnight. In the morning,

take out of freezer, stir for 2 hrs, TLC shows completion. Workup done with 5% citric acid,

saturated NaHCO$_3$, then dry with brine and MgSO$_4$. The reaction mixture was concentrated

and chromatographed on a Monster Pipette column in 1:1 hexane: EtOAc then 7:3 hexane:

EtOAc to avail compound 19 (28 mg , 67%) ^{1}H NMR (CDCl$_3$): δ 7.37 (d, 2H), 7.20 (m,

15H), 6.90 (d, 2H), 5.07-4.93 (m, 4H), 4.16 (brs, 1H), 3.80 (s, 3H), 3.75-3.37 (m, 4H), 3.36

(d, 1H), 3.20-2.93 (m, 6H), 2.80- 2.75 (dd, 1H).

Example 14

Compound 19 (28 mg, 0.35 mmol) was stirred in 4 mL DCM with addition of 1 mL TFA.

Stir for 45 minutes, at which time complete deprotection was noted by TLC as well as MS.

Azeotrope with toluene. The residue was dissolved in 1 mL CH$_3$CN, cooled to 0°C. Bis-

Furan *para*-Nitro phenol carbonate 11 (12 mg, 0.038 mmol), dimethyl amino pyridine (~ 1 mg, 0.008 mmol) and diisopropylethylamine (0.018 mL, 0.103 mmol) were added. The mixture was stirred and allowed to come to room temperature and stirred until TLC in 1:1 hexane:EtOAc showed completion. The reaction mixture was concentrated and the residue was partitioned between saturated NaHCO$_3$ and EtOAc. The organic layer was dried with brine and MgSO$_4$, then chromatographed on silica with hexane:EtOAc to afford compound 20 (20 mg, 67%). ^{1}NMR (CDCl$_3$): δ 7.76 (d, 2H), 7.34–7.16 (m, 15 H), 7.07 (d, 2H), 5.56 (d, 1H), 5.09 (m, 4H), 4.87 (m, 1H), 4.01 (m, 1H), 3.91 (m, 2H), 3.87 (s, 3H), 3.86 (m, 1H), 3.69 (m, 1H), 3.67 (m, 1H) 3.60 (d, 2H) 3.28 (m, 1H) 3.25 (d, 2H), 3.32 (d, 1H), 3.13 (m, 1H), 3.02 (m, 1H) 2.85 (d, 1H), 2.83 (m, 1H) 2.52 (m, 1H) 1.47 (m, 1H), 1.31 (m, 1H) 0.98 (s, 3H), 0.95 (s,3H).

Example 15

Compound 20 (7 mg, 0.008 mmol) was treated in a manner identical to example 8 to afford compound 21 (5 mg, 90%) ^{1}H NMR (CDCl$_3$): δ 7.80 (d, 2H), 7.25–7.16 (m, 5H), 7.09 (d, 2H), 5.58 (d, 1H), 4.92 (m, 1H), 3.99 (m, 1H), 3.92 (m, 1H), 3.88 (s, 3H), 3.86 (m, 1H), 3.77 (m, 1H), 3.75 (m, 1H), 3.73 (m, 1H), 3.71 (m, 1H) 3.71 (m, 1H), 3.68 (m, 1H), 3.57 (d,1H), 3.41 (d, 1H), 3.36 (m, 1H), 3.29 (d, 1H), 3.25 (d, 2H), 3.18 (m, 1H), 3.12 (m, 1H), 3.01 (d, 1H) 2.86 (m, 1H), 2.53 (m, 1H) 1.50 (m, 1H), 1.33 (m, 1H), 1.02 (s, 3H), 0.99 (s, 3H).

Example 16

Compound 15 (1.86 g, 9.20 mmol) was treated with triflate 22 in a manner identical to example 10 to afford compound 23 (0.71 g, 21.8%) ^{1}H NMR (CDCl$_3$): δ 5.21 (brs, 1H) 4.16-4.07 (m, 4H), 3.71-3.69 (d, 2H), 3.24 (s, 2H), 1.43 (s, 9H), 1.34-1.28 (m, 6H) 0.86 (s, 6H).

Example 17

Compound 23 (151 mg, 0.427 mmol) was dissolved in 10 mL DCM and 1.0 mL TFA was added. The reaction was stirred until completion. The reaction was azeotroped with toluene and the residue was then dissolved in THF and treated with basic Dowex resin beads. Afterwards, the beads were filtered away and solvent was removed to avail compound 24 (100 mg, 92%) ^{1}H NMR (CDCl$_3$): δ 4.15-4.05 (m, 4H), 3.72-3.69 (d, 2H), 3.27 (s, 2H), 1.30-1.26 (m, 6H) 0.81 (s, 6H).

Example 18

Compound 24 (100 mg, 0.395 mmol) was treated in a manner identical to example 12 to avail compound 25 (123 mg, 60%). ^{1}H NMR (CDCl$_3$): δ 7.26–7.13 (m, 5H), 4.48-4.83 (d, 1H)

5   4.17-4.06 (m, 4H), 3.75 (d, 2H) 3.56 (brs, 1H), 3.33 (s, 2H), 2.93-2.69 (m, 4H), 2.44-2.55 (dd, 2H) 1.32 (m, 6H), 0.916 (s, 6H).

Example 19

Compound 25 (88 mg, 0.171 mmol) was treated in a manner identical to example 13 to afford

10   compound 26 (65 mg, 55%) ^{1}H NMR (CDCl$_3$): δ 7.26–7.13 (m, 5H), 4.48-4.83 (d, 1H) 4.17-4.06 (m, 4H), 3.75 (d, 2H) 3.56 (brs, 1H), 3.33 (s, 2H), 2.93-2.69 (m, 4H), 2.44-2.55 (dd, 2H) 1.32 (m, 6H), 0.916 (s, 6H).

Example 20

15   Compound 26 (65 mg, 0.171 mmol) was treated in a manner identical to example 14 to afford compound 27 (49 mg, 70%) ^{1}H NMR:
(CDCl$_3$):δ 7.75 (d, 2H), 7.25–7.24 (m,4 H), 7.18 (m, 1H) 6.99 (d, 2H), 5.63 (d, 1H), 5.01 (m, 1H), 4.16 (m, 4H), 3.94 (m, 1H), 3.88 (m, 1H), 3.88 (s, 3H), 3.84 (m, 1H), 3.81 (m, 1H), 3.74 (m, 2H),), 3.70 (m, 1H), 3.69 (m, 1H) 3.43 (m, 1H), 3.24 (m, 1H), 3.22 (m, 2H) 3.21 (m,

20   2H) 3.12 (m, 1H), 3.02 (m, 1H) 2.86 (m, 1H), 2.72 (m, 1H), 1.54 (m, 1H), 1.38 (m, 1H) 1.35 (m, 6H) 1.00 (s, 3H), 0.96 (s,3H).

Example 21

Boc protected amine 28 (103 mg, 0.153 mmol) was dissolved in DCM (5 mL). The stirred

25   solution was cooled to 0°C. BBr$_3$ as a 1.0 M solution in DCM (0.92 mL, 0.92 mmol) was added dropwise over 10 min, and the reaction was allowed to continue stirring at 0°C for 20 min. The reaction was warmed to room temperature and stirring was continued for 2 hours. The reaction was then cooled to 0°C and quenched by dropwise addition of MeOH (1 mL). The reaction mixture was evaporated and the residue suspended in methanol which was

30   removed under reduced pressure. The procedure was repeated for EtOAc and finally toluene to afford free amine HBr salt 29 (107 mg, >100%) which was used without further purification.

Example 22

Amine HBr salt 29 (50 mg, 0.102 mmol) was suspended in 2 mL CH$_3$CN with stirring then cooled to 0°C. DMAP (25 mg, 0.205 mmol) was added, followed by Carbonate 11. The reaction was stirred at 0°C for 1.5 hrs then allowed to warm to room temperature. The

5 reaction was stirred overnight. A few drops Acetic acid were added to the reaction mixture, which was concentrated and re-diluted with ethyl acetate, shaken with 10% citric acid then saturated NaHCO$_3$. The organic layer was dried with brine and MgSO$_4$ and eluted on silica to afford di-phenol 30 (16 mg, 28%) ^{1}H NMR (CD$_3$OD): δ 7.61, (d, 2H), 7.01 (d, 2H), 6.87 (d, 2H), 6.62 (d, 2H), 5.55 (d, 1H), 4.93 (m, 1H), 3.92 (m, 2H), 3.79 (m, 5H), 3.35 (m, 1H), 3.07

10 (m, 2H), 2.88 (m, 3H), 2.41 (m, 1H), 2.00 (m, 1H), 1.54 (m, 1H), 1.31 (dd, 1H) 0.89-0.82 (dd, 6H).

Example 23

A solution of di-phenol 30 (100 mg, 0.177 mmol) was made in CH$_3$CN that had been dried

15 over K$_2$CO$_3$. To this, the triflate (0.084 mL, 0.23 mmol) was added, followed by Cs$_2$CO$_3$ (173 mg, 0.531 mmol). The reaction was stirred for 1 hr. TLC (5% IprOH/DCM) showed 2 spots with no starting materials left. Solvent was evaporated and the residue was partitioned between EtOAc and water. The organic layer was washed with saturated NaHCO$_3$, then dried with brine and MgSO$_4$. The mixture was separated by column chromatography on

20 silica with 3% IprOH in DCM. The upper spot 31 (90 mg, 46%) was confirmed to be the *bis* alkylation product. The lower spot required further purification on silica gel plates to afford a single *mono* alkylation product 32 (37 mg, 26%). The other possible alkylation product was not observed. NMR : ^{1}H NMR (CDCl$_3$):*for 31:* δ 7.57 (d, 2H), 7.37 (m, 10H) 7.03 (d, 2H), 6.99 (d, 2H), 6.73 (d, 2H), 5.69 (d, 1H), 5.15-5.09 (m, 4H), 5.10 (m, 1H), 4.32 (d, 2H),

25 4.02 (d, 1H), 3.82 (m, 1H) 3.81 (m, 1H), 3.93-3.81 (m, 2H), 3.74 (d, 1H), 3.06 (m, 1H), 3.00 (m, 1H), 2.96 (m, 1H), 2.91 (m, 1H) 2.77 (m, 1H) 2.64 (m, 1H) 2.47 (m, 1H) 1.82 (m, 2H) 1.79 (m, 1H), 0.94-0.86 (dd, 6H)*for 32:* δ 7.68 (d, 2H), 7.33-7.35 (m, 20H), 7.11 (d, 2H), 6.96 (d, 2H), 6.80 (d, 2H), 5.26 (d, 1H), 5.11(m, 8H), 5.00 (m, 1H) 4.23 (d, 2H), 4.19 (d, 2H), 3.93 (m, 1H), 3.82-3.83 (m, 3H), 3.68-3.69 (m, 2H) 3.12-2.75 (m, 7H), 1.82 (m, 1H),

30 1.62-1.52 (d, 2H), 0.89-0.86 (dd, 6H).

Example 24

Ref: J. Med. Chem. 1992, 35 10,1681-1701

To a solution of phosphonate 32 (100 mg, 0.119 mmol) in dry dioxane was added Cs$_2$CO$_3$ (233 mg, 0.715 mmol), followed by 2-(dimethylamino) ethyl chloride hydrochloride salt (69 mg, 0.48 mmol). The reaction was stirred at room temperature and monitored by TLC. When it was determined that starting material remained, additional Cs$_2$CO$_3$ (233 mg, 0.715

5   mmol) as well as amine salt (69 mg, 0.48 mmol) were added and the reaction was stirred overnight at 60°C. In the morning when TLC showed completion the reaction was cooled to room temperature, filtered, and concentrated. The product amine 33 (40 mg, 37%) was purified on silica. Decomposition was noted as lower spots were seen to emerge with time using 15% MeOH in DCM on silica.

10

Example 25:

Amine 33 (19 mg, 0.021 mmol) was dissolved in 1.5 mL DCM. This solution was stirred in an icebath. Methane sulfonic acid (0.0015 mL, 0.023 mmol) was added and the reaction was stirred for 20 minutes. The reaction was warmed to room temperature and stirred for 1 hour.

15   The product, amine mesylate salt 34 (20 mg, 95%) was precipitated out by addition of hexane. ^{1}H NMR (CD$_3$OD): δ 7.69 (d, 2H), 7.35 (m, 10H), 7.15 (m, 4H) 6.85 (m, 2H), 5.49 (d, 1H), 5.10 (m, 4H), 4.83 (m, 1H), 4.62 (d, 2H), 4.22 (m, 2H), 3.82 (m, 1H), 3.56 (m, 1H), 3.48 (m, 2H), 3.35 (m, 1H), 2.99 (m, 1H), 2.95 (m, 1H), 2.84 (s, 6H), 2.78 (m, 1H), 2.75 (m, 1H), 2.70 (m, 1H), 2.40 (m, 1H) 1.94 (m, 1H), 1,43 (m, 1H), 1.27 (m, 1H), 0.77 (dd, 6H).

Example Section E

Scheme 1
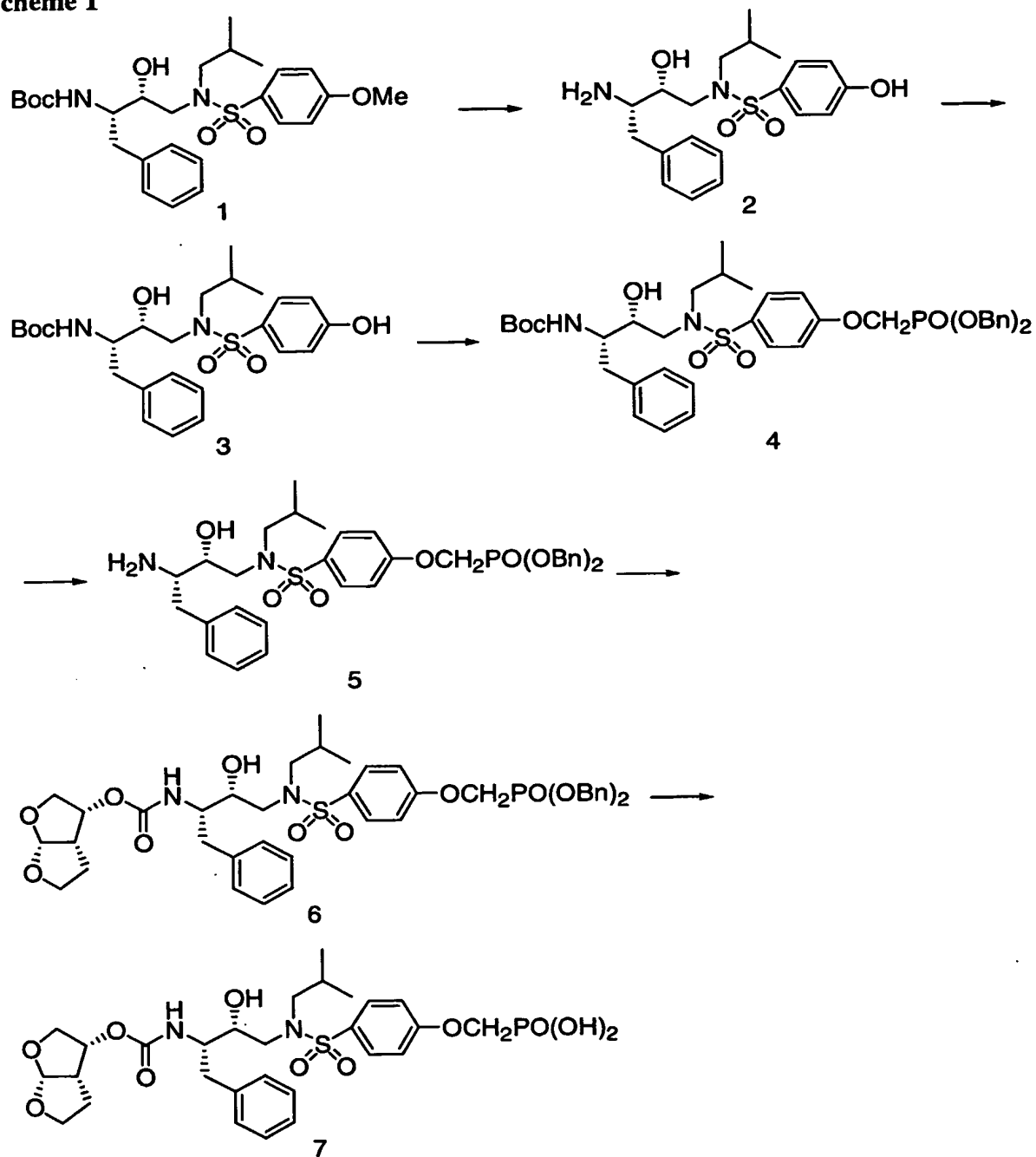
Example 1

To a solution of phenol 3 (336 mg, 0.68 mmol) in THF (10 mL) was added Cs_2CO_3 (717 mg,

2.2 mmol) and triflate (636 mg, 1.5 mmol) in THF (3 mL). After the reaction mixture was

stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and

5   water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced

pressure. The crude product was chromatographed on silica gel (eluting 40-50%

EtOAc/hexane) to give dibenzylphosphonate 4 (420 mg, 80%) as a colorless oil.

Example 2

10
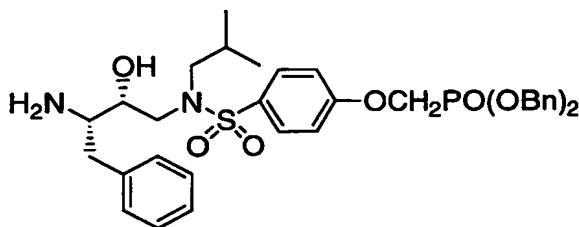
To a solution of dibenzylphosphonate 4 (420 mg, 0.548 mmol) in CH_2Cl_2 (10 mL) was added

TFA (0.21 mL, 2.74 mmol). After the reaction mixture was stirred for 2 h at room

temperature, additional TFA (0.84 mL, 11 mmol) was added and the mixture was stirred for 3

h. The reaction mixture was evaporated under reduced pressure and the residue was

15   partitioned between EtOAc and 1M $NaHCO_3$. The organic phase was dried over Na_2SO_4,

filtered, and evaporated under reduced pressure to give amine 5 (325 mg, 89%).

Example 3
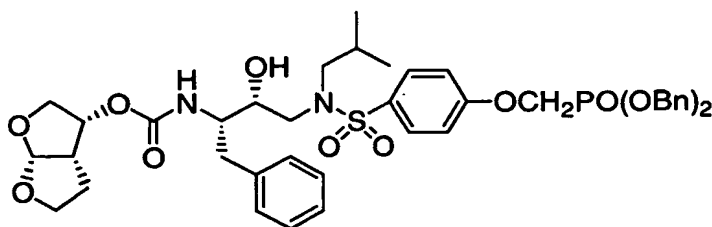
20   To a solution of carbonate (79 mg, 0.27 mmol), amine 5 (178 mg, 0.27 mmol), and CH_3CN

(10 mL) was added DMAP (66 mg, 0.54 mmol) at 0°C. After the reaction mixture was

warmed to room temperature and stirred for 16 hours, the mixture was concentrated under

reduced pressure. The residue was chromatographed on silica gel (eluting 60-90%

EtOAc/hexane) to give a mixture of carbamate 6 and starting carbonate. The mixture was

25   further purified by HPLC on C18 reverse phase chromatography (eluting 60% CH_3CN/water)

to give carbamate **6** (49 mg, 22%) as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.68 (d, 2H), 7.22 (m, 15 H), 6.95 (d, 2H), 5.62 (d, 1H), 5.15 (dt, 4H), 5.00 (m, 2H), 4.21 (d, 2H), 3.88 (m, 4H), 3.67 (m, 3H), 3.15 (m, 2H), 2.98 (m, 3H), 2.80 (m, 2H), 1.82 (m, 1H), 1.61 (m, 1H), 0.93 (d, 3H), 0.88 (d, 3H).

5

Example 4
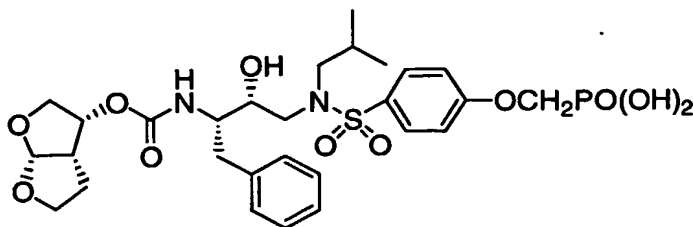
To a solution of carbamate **6** (21 mg, 0.026 mmol) in EtOH / EtOAc (2 mL/1 mL) was added 10% Pd/C (11 mg). After the reaction mixture was stirred under H$_2$ atmosphere (balloon) for 2 hours, the mixture was filtered through Celite. The filtrate was evaporated under reduced pressure to give phosphonic acid **7** (17 mg, 100%) as a colorless solid. ^{1}H NMR (300 MHz, CD$_3$OD) δ 7.73 (d, 2H), 7.19 (m, 5H), 7.13 (d, 2H), 5.53 (d, 1H), 4.26 (d, 2H), 3.86 (m, 1H), 3.64 (m, 5H), 3.38 (d, 1H), 3.13 (d, 1H), 3.03 (dd, 1H), 2.86 (m, 3H), 2.48 (m, 1H), 1.97 (m, 1H), 1.47 (m, 1H), 1.28 (m, 2H), 1.13 (t, 1H), 0.88 (d, 3H), 0.83 (d, 3H).

Scheme 2

8

9
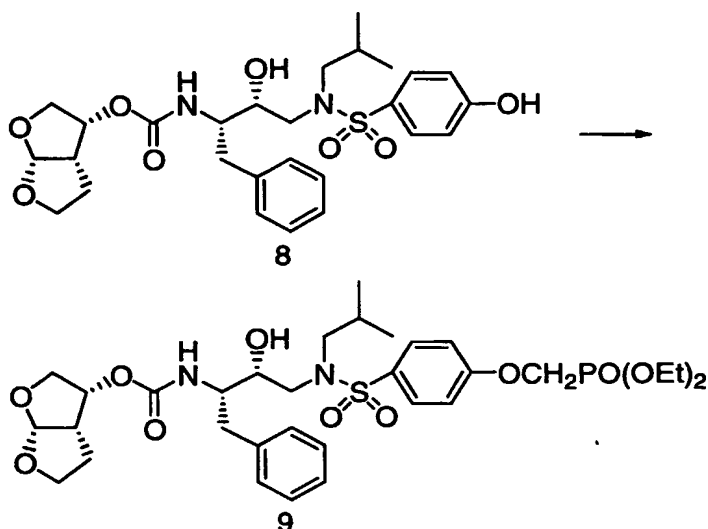
<u>Example 5</u>
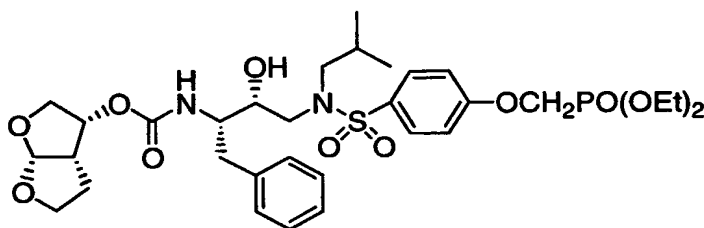
To a solution of phenol **8** (20 mg, 0.036 mmol) and triflate (22 mg, 0.073 mmol) in THF (2 mL) was added Cs_2CO_3 (29 mg, 0.090 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography (eluting 80% EtOAc/hexane) to give diethylphosphonate **9** (21 mg, 83%) as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.73 (d, 2H), 7.25 (m, 5H), 7.07 (d, 2H), 5.64 (d, 1H), 5.01 (m, 2H), 4.25 (m, 6H), 3.88 (m, 4H), 3.70 (m, 3H), 2.97 (m, 6H), 1.70 (m, 4H), 1.38 (t, 6H), 0.92 (d, 3H), 0.88 (d, 3H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 18.1.

Scheme 3
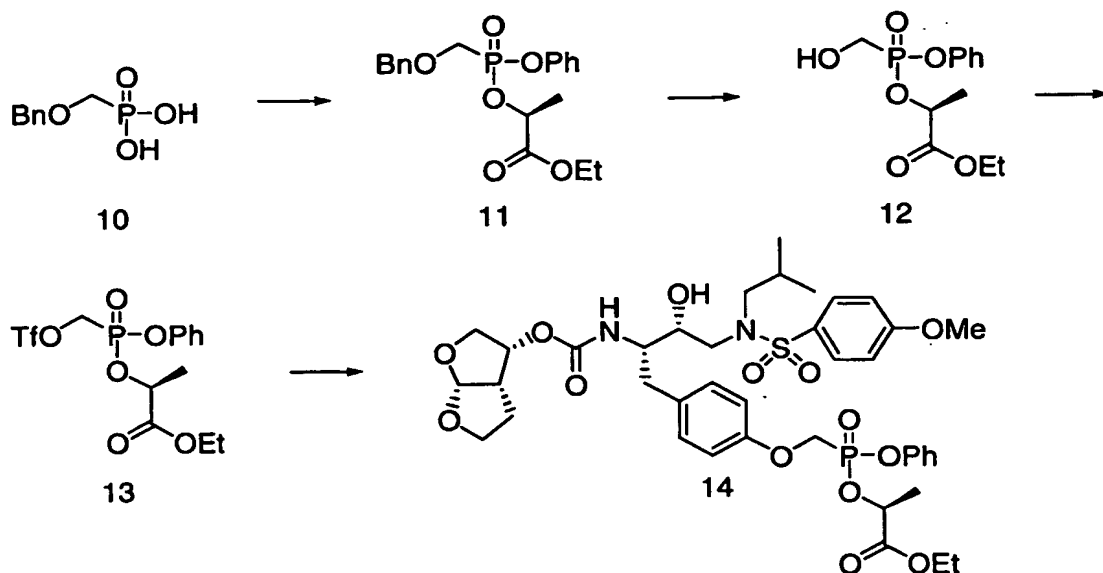
Example 6
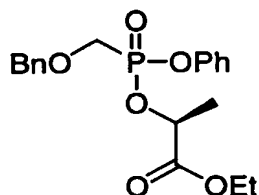
To a solution of phosphonic acid **10** (520 mg, 2.57 mmol) in CH_3CN (5 mL) was added thionyl chloride (0.75 mL, 10.3 mmol) and heated to 70°C in an oil bath. After the reaction mixture was stirred for 2 h at 70°C, the mixture was concentrated and azeotroped with toluene. To a solution of the crude chloridate in toluene (5 mL) was added tetrazole (18 mg, 0.26 mmol) at 0°C. To this mixture was added phenol (121 mg, 1.28 mmol) and triethylamine (0.18 mL, 1.28 mmol) in toluene (3 mL) at 0°C. After the reaction mixture was warmed to room temperature and stirred for 2 h, ethyl lactate (0.29 mL, 2.57 mmol) and triethylamine (0.36 mL, 2.57 mmol) in toluene (2.5 mL) were added. The reaction mixture was stirred for 16 hours at room temperature, at which time the mixture was partitioned between EtOAc and sat. NH_4Cl. The organic phase was washed with sat. NH_4Cl, 1M $NaHCO_3$, and brine, then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 20-40% EtOAc/hexane) to give two diastereomers of phosphonate **11** (66 mg, 109 mg, 18% total) as colorless oils.

Example 7A
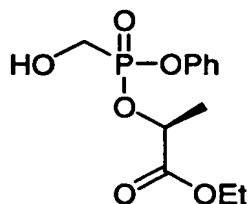
To a solution of phosphonate **11** isomer A (66 mg, 0.174 mmol) in EtOH (2 mL) was added

5   10% Pd/C (13 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for

6 h, the mixture was filtered through Celite. The filtrate was evaporated under reduced

pressure to give alcohol **12** isomer A (49 mg, 98%) as a colorless oil.

Example 7B

10   To a solution of phosphonate **11** isomer B (110 mg, 0.291 mmol) in EtOH (3 mL) was added

10% Pd/C (22 mg). After the reaction mixture was stirred under H_2 atmosphere (balloon) for

6 h, it was filtered through Celite. The filtrate was evaporated under reduced pressure to give

alcohol **12** isomer B (80 mg, 95%) as a colorless oil.

15   Example 8A
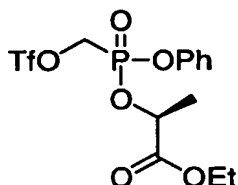
To a solution of alcohol **12** isomer A (48 mg, 0.167 mmol) in CH_2Cl_2 (2 mL) was added 2,6-

lutidine (0.03 mL, 0.250 mmol) and trifluoromethanesulfonic anhydride (0.04 mL, 0.217

20   mmol) at -40°C (dry ice-CH_3CN bath). After the reaction mixture was stirred for 15 min at -

40°C, the mixture was warmed to 0°C and partitioned between Et_2O and 1M H_3PO_4. The

organic phase was washed with 1M H_3PO_4 (3 times), dried over Na_2SO_4, filtered, and

evaporated under reduced pressure to give triflate **13** isomer A (70 mg, 100%) as a pale

yellow oil.

25

Example 8B

To a solution of alcohol 12 isomer B (80 mg, 0.278 mmol) in CH$_2$Cl$_2$ (3 mL) was added 2,6-lutidine (0.05 mL, 0.417 mmol) and trifluoromethanesulfonic anhydride (0.06 mL, 0.361 mmol) at -40°C (dry ice-CH$_3$CN bath). After the reaction mixture was stirred for 15 min at -40°C, the mixture was warmed to 0°C and partitioned between Et$_2$O and 1M H$_3$PO$_4$. The organic phase was washed with 1M H$_3$PO$_4$ (3 times), dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure to give triflate 13 isomer B (115 mg, 98%) as a pale yellow oil.

Example 9A
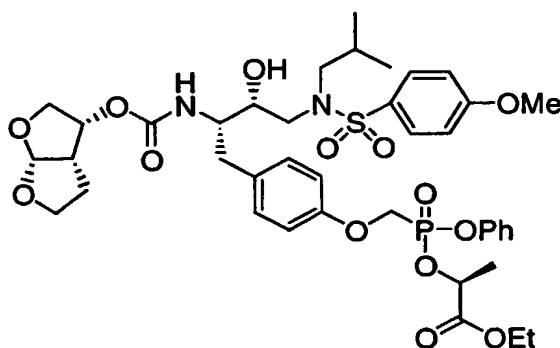
To a solution of phenol (64 mg, 0.111 mmol):
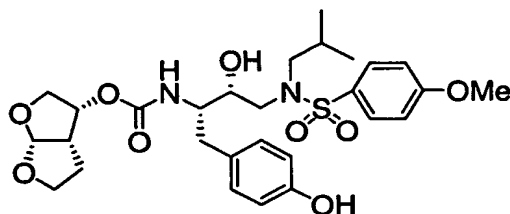
and triflate 13 isomer A (70 mg, 0.167 mmol) in THF (2 mL) was added Cs$_2$CO$_3$ (72 mg, 0.222 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 60-80% EtOAc/hexane) to give a mixture. The mixture was further purified by HPLC on C18 reverse phase chromatography (eluting 55% CH$_3$CN/water) to give phosphonate 14 isomer A (30 mg, 32%) as a colorless solid. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.71 (d, 2H), 7.26 (m, 6H), 7.00 (m, 5H), 5.65 (d, 1H), 5.14 (m, 1H), 5.00 (m, 2H), 4.54 (dd, 1H), 4.44 (dd, 1H), 4.17 (m, 2H), 3.96 (dd, 1H), 3.86 (m, 5H), 3.72

(m, 3H), 3.14 (m, 1H), 2.97 (m, 4H), 2.79 (m, 2H), 1.83 (m, 1H), 1.62 (m, 3H), 1.50 (d, 3H), 1.25 (m, 3H), 0.93 (d, 3H), 0.88 (d, 3H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 17.4.

Example 9B

To a solution of phenol (106 mg, 0.183 mmol):
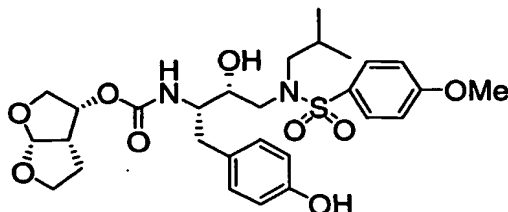
and triflate 13 isomer B (115 mg, 0.274 mmol) in THF (2 mL) was added Cs$_2$CO$_3$ (119 mg, 0.366 mmol). After the reaction mixture was stirred for 30 min at room temperature, the mixture was partitioned between EtOAc and water. The organic phase was dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was chromatographed on silica gel (eluting 60-80% EtOAc/hexane) to give a mixture. The mixture was further purified by HPLC on C18 reverse phase chromatography (eluting 55% CH$_3$CN/water) to give phosphonate 14 isomer B (28 mg, 18%) as a colorless solid. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.71 (d, 2H), 7.26 (m, 6H), 6.94 (m, 5H), 5.66 (d, 1H), 5.17 (m, 1H), 4.99 (m, 2H), 4.55 (m, 1H), 4.42 (m, 1H), 4.16 (m, 2H), 3.97 (m, 1H), 3.85 (m, 5H), 3.72 (m, 3H), 3.13 (m, 1H), 2.97 (m, 4H), 2.80 (m, 2H), 1.83 (m, 1H), 1.60 (m, 6H), 1.22 (m, 3H), 0.93 (d, 3H), 0.88 (d, 3H). ^{31}P NMR (300 MHz, CDCl$_3$) δ 15.3.

Resolution of Compound 14 Diastereomers

Analysis was performed on an analytical Alltech Econosil column, conditions described below, with a total of about 0.5 mg 14 injected onto the column. This lot was a mixture of major and minor diastereomers where the lactate ester carbon is a mix of R and S configurations. Up to 2 mg could be resolved on the analytical column. Larger scale injections (up to 50 mg 14) were performed on an Alltech Econosil semi-preparative column, conditions described below.

The isolated diastereomer fractions were stripped to dryness on a rotary evaporator under house vacuum, followed by a final high vacuum strip on a vacuum pump. The

chromatographic solvents were displaced by two portions of dichloromethane before the final high vacuum strip to aid in removal of trace solvents, and to yield a friable foam.

5 The bulk of the diastereomer resolution was performed with *n*-heptane substituted for hexanes for safety considerations.

Sample Dissolution: While a fairly polar solvent mixture is described below, the sample may be dissolved in mobile phase with a minimal quantity of ethyl alcohol added to dissolve the sample.

10

Analytical Column, 0.45 mg Injection, Hexanes – IPA (90:10)

411
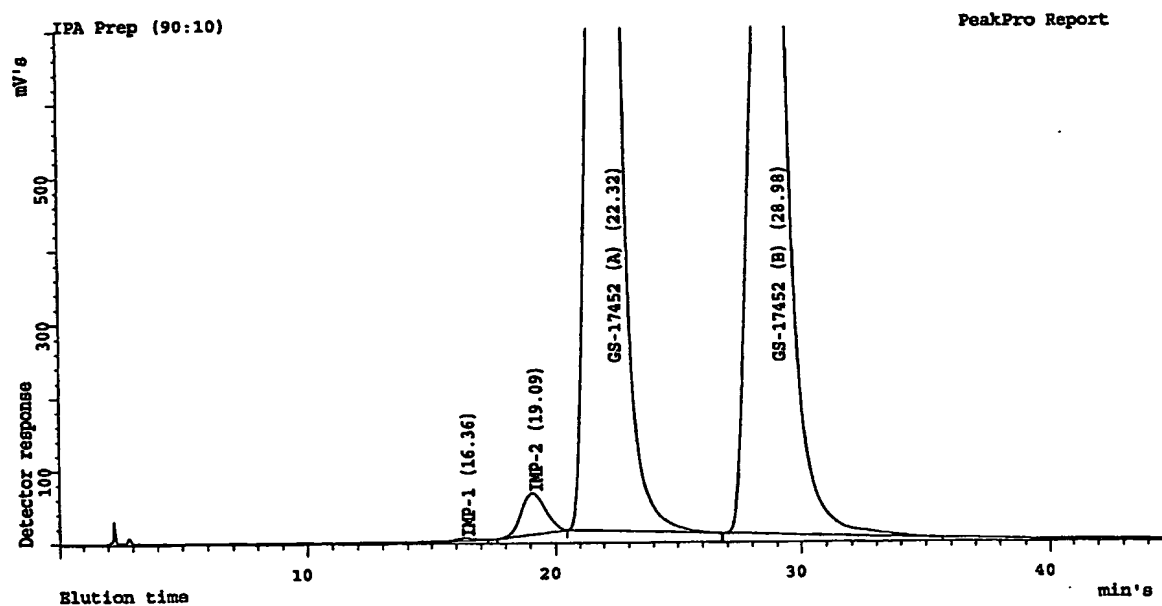
HPLC CONDITIONS

Column	:	Alltech Econosil, 5 μm, 4.6 x 250 mm
Mobile Phase	:	Hexanes – Isopropyl Alcohol (90:10)
Flow Rate	:	1.5 mL/min
Run Time	:	50 min
Detection	:	UV at 242 nm
Temperature	:	Ambient
Injection Size	:	100 μL
Sample Prep.	:	~ 5 mg/mL, dissolved in hexanes – ethyl alcohol (75:25)
Retention Times	:	**14 ~ 22** min
	:	**14 ~ 29** min
	:	Less Polar Impurity ~ 19 min

Semi-Preparative Column, 50 mg Injection, *n*-Heptane – IPA (84:16)
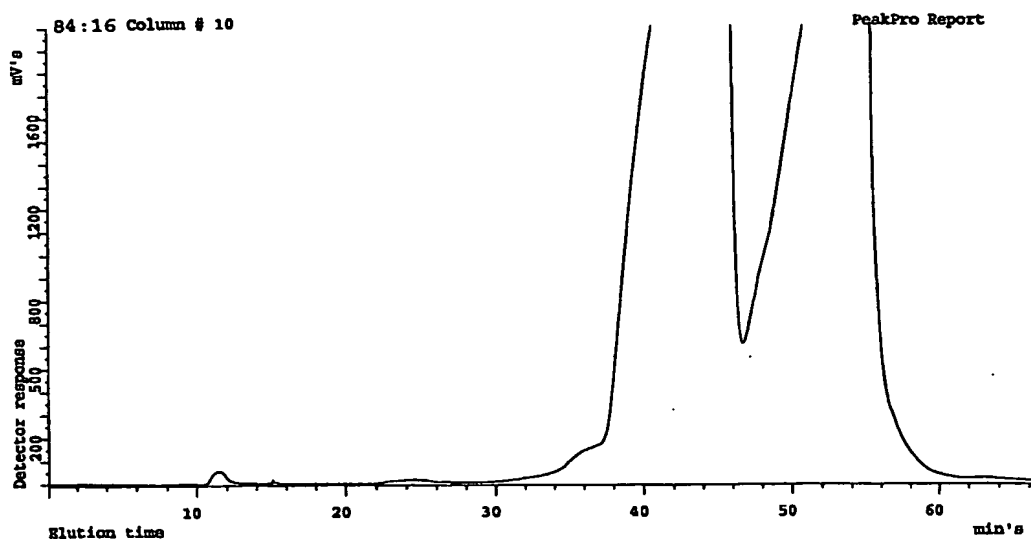
HPLC CONDITIONS

Column	: Alltech Econosil, 10 µm, 22 x 250 mm
Mobile Phase	: *n*-Heptane – Isopropyl Alcohol (84:16)
Flow Rate	: 10 mL/min
Run Time	: 65 min
Detection	: UV at 257 nm
Temperature	: Ambient
Injection Size	: ~50 mg
Dissolution	: 2 mL mobile phase plus ~ 0.75 mL ethyl alcohol
Retention Times	: **14 ~ 41 min**
	: **14 ~ 54 min**
	: Less Polar Impurity ~ Not resolved

Example Section F

Example 1

Phosphonic acid 2: To a solution of compound 1 (A. Flohr et al, J. Med. Chem., 42, 12,

5   1999; 2633-2640) (4.45 g, 17 mmol) in CH_2Cl_2 (50 mL) at room temperature was added

bromotrimethylsilane (1.16 mL, 98.6 mmol). The solution was stirred for 19 h. The volatiles

were evaporated under reduced pressure to give the oily phosphonic acid 2 (3.44 g, 100%).

^1H NMR ($CDCl_3$) δ 7.30 (m, 5H), 4.61 (s, 2 H), 3.69 (d, 2H).

10   Example 2

Compound 3: To a solution of phosphonic acid 2 (0.67 g, 3.3 mmol) in CH_3CN (5 mL) was

added thionyl chloride (1 mL, 13.7 mmol) and the solution was heated at 70°C for 2.5 h. The

volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily

phophonyl dichloride. The crude chloride intermediate was dissolved in CH_2Cl_2 (20 mL) and

15   cooled in an ice/water bath. Ethyl lactate (1.5 mL, 13.2 mmol) and triethyl amine (1.8 mL,

13.2 mmol) were added dropwise. The mixture was stirred for 4 h at room temperature and

dilluted with more CH_2Cl_2 (100 mL). The organic solution was washed with 0.1N HCl,

saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$) filtered and evaporated under reduced

pressure. The crude product was chromatographed on silica gel to afford oily compound 3

20   (0.548 g, 41%). ^1H NMR ($CDCl_3$) δ 7.30 (m, 5H), 5.00-5.20 (m, 2H), 4.65 (m, 2H), 4.20 (m,

4H), 3.90 (d, 2H), 1.52 (t, 6H), 1.20 (t, 6H).

Example 3

Alcohol 4: A solution of compound 3 (0.54 g, 1.34 mmol) in EtOH (15 mL) was treated with

25   10% Pd/C (0.1 g) under H_2 (100 psi) for 4 h. The mixture was filtered and the filtrate was

treated with fresh 10% PD/C (0.1 g) under H_2 (1 atmosphere) for 18 h. The mixture was

filtered and the filtrate was evaporated to afford alcohol 4 (0.395 g, 94%) as an oil. ^1H NMR

($CDCl_3$) δ 4.90-5.17 (m, 2H), 4.65 (q, 2H), 4.22 (m, 4H), 4.01 (m, 2H), 1.55 (t, 6H), 1.21 (t,

6H); ^{31}P NMR ($CDCl_3$) δ 22.8.

30

Example 4

Triflate 5: To a solution of alcohol 4 (122.8 mg, 0.393 mmol) in CH_2Cl_2 (5 mL) at -40°C

were added 2,6-lutidine (0.069 mL, 0.59 mmol) and trifluoromethansulfonic anhydride

(0.086 mL, 0.51 mmol). Stirring was continued at 0°C for 2 h. and the mixture partitioned in CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product 5 (150 mg, 87%) was used for the next step without further purification. ^{1}H NMR (CDCl$_3$) δ

5   5.0-5.20 (m, 2H), 4.93 (d, 2H), 4.22 (m, 4H), 1.59 (m, 6H), 1.29 (t, 6H).

Example 5

Phosphonate 6: A solution of phenol 8 (see Scheme Section A, Scheme 1 and 2) (32 mg, 0.055 mmol) and triflate 5 (50 mg, 0.11 mmol) in THF (1.5 mL) at room temperature was

10   treated with Cs$_2$CO$_3$ (45.6 mg, 0.14 mmol). The mixture was stirred for 2.5 h and partitioned in EtOAc and saturated NaHCO$_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30-70% EtOAc/hexane) affording the phosphonate 6 (41 mg, 84%) as a solid. ^{1}H NMR (CDCl$_3$) δ 7.71 (d, 2H), 7.13 (d, 2H), 7.00

15   (d, 2H), 6.90 (d, 2H), 5.65 (d, 1H), 4.90-5.22 (m, 3H), 4.40 (m, 2H), 4.20 (m, 4H), 3.90 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 1.52-1.87 (m, 12H), 1.25 (m, 6H), 0.85-0.90 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 20.0.

Example 6

20   Compound 7: To a solution of phosphonic acid 2 (0.48 g, 2.37 mmol) in CH$_3$CN (4 mL) was added thionyl chloride (0.65 mL, 9.48 mmol) and the solution was heated at 70°C for 2.5 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily phophonyl dichloride. The crude chloride intermediate was dissolved in CH$_2$Cl$_2$ (5 mL) and cooled in an ice/water bath. Ethyl glycolate (0.9 mL, 9.5 mmol) and triethyl amine (1.3 mL, 9.5

25   mmol) were added dropwise. The mixture was stirred for 2 h at room temperature and dilluted with more CH$_2$Cl$_2$ (100 mL). The organic solution was washed with 0.1N HCl, saturated aqueous NaHCO$_3$, and saturated NaCl, dried (MgSO$_4$) filtered and concentrated under reduced pressure. The crude product was chromatographed on silica gel to afford oily compound 7 (0.223 g, 27%). ^{1}H NMR (CDCl$_3$) δ 7.30 (m, 5H), 4.65 (m, 6H), 4.25 (q, 4H), 3.96 (d, 2H),

30   1.27 (t, 6H); ^{31}P NMR (CDCl$_3$) δ 24.0.

Example 7

Alcohol 8: A solution of compound 7 (0.22 g, 0.65 mmol) in EtOH (8 mL) was treated with 10% Pd/C (0.04 g) under H_2 (1 atmosphere) for 4 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 8 (0.156 g, 96%) as an oil. ^{1}H NMR (CDCl$_3$) δ 4.66 (m, 4H), 4.23 (q, 4H), 4.06 (d, 2H), 1.55 (t, 6H), 1.26 (t, 6H); ^{31}P NMR (CDCl$_3$) δ 26.8.

Example 8

Triflate 9: To a solution of alcohol 8 (156 mg, 0.62 mmol) in CH$_2$Cl$_2$ (5 mL) at -40°C were added 2,6-lutidine (0.11 mL, 0.93 mmol) and trifluoromethansulfonic anhydride (0.136 mL, 0.8 mmol). Stirring was continued at 0°C for 2 h. and the mixture partitioned in CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product 9 (210 mg, 88%) was used for the next step without further purification. ^{1}H NMR (CDCl$_3$) δ 4.90 (d, 2H), 4.76 (d, 4H), 4.27 (q, 4H), 1.30 (t, 6H).

Example 9

Phosphonate 10: A solution of phenol 8 (30 mg, 0.052 mmol) and triflate 9 (30 mg, 0.078 mmol) in THF (1.5 mL) at room temperature was treated with Cs$_2$CO$_3$ (34 mg, 0.1 mmol). The mixture was stirred for 2.5 h and partitioned in EtOAc and saturated NaHCO$_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30-70% EtOAc/hexane) affording the unreacted phenol (xx) (12 mg, 40%) and the phosphonate 10 (16.6 mg, 38%) as a solid. ^{1}H NMR (CDCl$_3$) δ 7.71 (d, 2H), 7.13 (d, 2H), 7.00 (d, 2H), 6.90 (d, 2H), 5.65 (d, 1H), 5.00 (m, 2H), 4.75 (m, 4H), 4.48 (d, 2H), 4.23 (q, 4H), 3.90 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 2.23 (b.s., 2H), 1.52-1.87 (m, 4H), 1.25 (t, 6H), 0.85-0.90 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 22.0.

Example 10

Compound 11: To a solution of phosphonic acid 2 (0.512 g, 2.533 mmol) in CH$_3$CN (5 mL) was added thionyl chloride (0.74 mL, 10 mmol) and the solution was heated at 70°C for 2.5 h. The volatiles were evaporated under reduced pressure and dried in vacuo to afford an oily phophonyl dichloride. The crude chloride intermediate was dissolved in toluene (8 mL) and cooled in an ice/water bath. A catalytic amount of tetrazol (16 mg, 0.21 mmol) was added followed by the addition of a solution of triethylamine (0.35 mL, 2.53 mmol) and phenol (238

mg, 2.53 mmol) in toluene (5 mL). The mixture was stirred at room temperature for 3 h. A solution of ethyl glycolate (0.36 mL, 3.8 mmol) and triethyl amine (0.53 mL, 3.8 mmol) in toluent (3 mL) was added dropwise. The mixture was stirred for 18 h at room temperature and partitioned in EtOAc and 0.1N HCl. The organic solution was washed with saturated

5   aqueous NaHCO$_3$, and saturated NaCl, dried (MgSO$_4$) filtered and concentrated under reduced pressure. The crude product was chromatographed on silica gel to afford diphenyl phophonate as a byproduct (130 mg) and compound 11 (0.16 g, 18%). ^{1}H NMR (CDCl$_3$) δ 7.15-7.40 (m, 10H), 4.58-4.83 (m, 4H), 4.22 (q, 2H), 4.04 (dd, 2H), 1.24 (t, 3H).

10   Example 11

Alcohol 12: A solution of compound 11 (0.16 g, 0.44 mmol) in EtOH (5 mL) was treated with 10% Pd/C (0.036 g) under H$_2$ (1 atmosphere) for 22 h. The mixture was filtered and the filtrate was evaporated to afford alcohol 12 (0.112 g, 93%) as an oil. ^{1}H NMR (CDCl$_3$) δ 7.15-7.36 (m, 5H), 4.81 (dd, 1H), 4.55 (dd, 1H), 4.22 (q, 2H), 4.12 (m, 2H), 3.78 (b.s., 1H),

15   1.26 (t, 6H); ^{31}P NMR (CDCl$_3$) δ 22.9

Example 12

Triflate 13: To a solution of alcohol 12 (112 mg, 0.41 mmol) in CH$_2$Cl$_2$ (5 mL) at -40°C were added 2,6-lutidine (0.072 mL, 0.62 mmol) and trifluoromethansulfonic anhydride (0.09

20   mL, 0.53 mmol). Stirring was continued at 0°C for 3 h. and the mixture partitioned in CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (30% EtOAc/hexane) affording triflate 13 (106 mg, 64%). ^{1}H NMR (CDCl$_3$) δ 7.36 (m, 2H), 7.25 (m, 3H), 4.80-5.10 (m, 3H), 4.60 (dd, 1H),

25   4.27 (q, 2H), 1.28 (t, 3H); ^{31}P NMR (CDCl$_3$) δ 11.1

Example 13

Phosphonate 14: A solution of phenol 8 (32 mg, 0.052 mmol) and triflate 13 (32 mg, 0.079 mmol) in CH$_3$CN (1.5 mL) at room temperature was treated with Cs$_2$CO$_3$ (34 mg, 0.1 mmol).

30   The mixture was stirred for 1 h and partitioned in EtOAc and saturated NaHCO$_3$. The organic layer was washed with saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (70%

EtOAc/hexane) affording phosphonate 14 (18 mg, 40%). ^{1}H NMR (CDCl$_3$) δ 7.71 (d, 2H), 6.75-7.35 (m, 11H, 5.65 (d, 1H), 5.00 (m, 2H), 4.50-4.88 (m, 3H), 4.20 (q, 2H), 3.84 (s, 3H), 3.65-4.00 (m, 5H), 2.70-3.20 (m, 6H), 1.52-1.87 (m, 6H), 1.25 (t, 3H), 0.85-0.90 (m, 6H); ^{31}P NMR (CDCl$_3$) δ 17.9, 17.7.

Example 14

Piperidine 16: A solution of compound 15 (3.1 g, 3.673 mmol) in MeOH (100 mL) was treated with 10% Pd/C (0.35 g) under H$_2$ (1 atmosphere) for 18 h. The mixture was filtered and the filtrate was evaporated to afford phenol 16 (2 g, 88%). ^{1}H NMR (CD$_3$OD) δ 7.76 (d, 2H), 7.08 (d, 2H), 7.04 (d, 2H), 6.65 (d, 2H), 5.59 (d, 1H), 4.95 (m, 1H), 3.98 (s, 3H), 3.65-4.00 (m, 5H), 3.30-3.50 (m, 3H), 2.80-3.26 (m, 5H), 2.40-2.70 (m, 3H), 1.35-2.00 (m, 7H), 1.16 (m, 2H); MS (ESI) 620 (M+H).

Example 15

Formamide 17: Piperidine 16 obtained above (193 mg, 0.3118 mmol) in DMF (4 mL) was treated with formic acid (0.035 mL, 0.936 mmol), triethylamine (0.173 mL, 1.25 mmol) and EDCI (179 mg, 0.936 mmol) at room temperature. The mixture was stirred for 18 h and partitioned in EtOAc and saturated NaHCO$_3$. The organic layer was washed with saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAC/hexane) affording formamide 17 (162 mg, 80%). ^{1}H NMR (CDCl$_3$) δ 7.96 (s, 1H), 7.68 (d, 2H), 7.04 (d, 2H), 6.97 (d, 2H), 6.76 (d, 2H), 5.63 (d, 1H), 5.37 (bs, 1H), 5.04 (m, 1H), 4.36 (m, 1H), 3.93 (s, 3H), 3.52-3.95 (m, 7H), 2.70-3.20 (m, 8H), 1.48-2.00 (m, 7H), 1.02 (m, 2H).

Example 16

Dibenzyl phosphonate 18: A solution of phenol 17 (123 mg, 0.19 mmol) and dibenzyl trifluoromethansulfonyloxymethanphosphonate YY (120 mg, 0.28 mmol) in CH$_3$CN (1.5 mL) at room temperature was treated Cs$_2$CO$_3$ (124 mg, 0.38 mmol). The mixture was stirred for 3 h and partitioned in CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO$_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% MeOH/CH$_2$Cl$_2$) affording phosphonate 18 (154 mg, 88%). ^{1}H NMR (CDCl$_3$) δ 7.96 (s, 1H), 7.68 (d, 2H), 7.35 (m, 10H), 7.10 (d, 2H), 6.97 (d, 2H), 6.80 (d, 2H), 5.63 (d, 1H), 4.96-5.24 (m, 6H), 4.37

(m, 1H), 4.20 (d, 2H), 3.84 (s, 3H), 3.52-3.95 (m, 7H), 2.55-3.20 (m, 8H), 1.48-2.00 (m, 7H), 1.02 (m, 2H). ^{31}P NMR (CDCl₃) δ 20.3.

Example 17

5   Phosphonic acid 19: A solution of phosphonate 18 (24 mg, 0.026 mmol) in MeOH (3 mL) was treated with 10% Pd/C (5 mg) under H₂ (1 atmosphere) for 4 h. The mixture was filtered and the filtrate was evaporated to afford phosphonic acid 19 as a solid (18 mg, 93%). ^{1}H NMR (CD₃OD) δ 8.00 (s, 1H), 7.67 (d, 2H), 7.18 (d, 2H), 7.09 (d, 2H), 6.90 (d, 2H), 5.60 (d, 1H), 4.30 (m, 1H), 4.16 (d, 2H), 3.88 (s, 3H), 3.60-4.00 (m, 7H), 3.04-3.58 (m, 5H), 2.44-

10   2.92 (m, 5H), 1.28-2.15 (m, 5H), 1.08 (m, 2H). ^{31}P NMR (CDCl₃) δ 16.3.

Example 18

Diethyl phosphonate 20: A solution of phenol 17 (66 mg, 0.1 mmol) and diethyl trifluoromethansulfonyloxymethanphosphonate XY (46 mg, 0.15mmol) in CH₃CN (1.5 mL) at

15   room temperature was treated Cs₂CO₃ (66 mg, 0.2 mmol). The mixture was stirred for 3 h and partitioned in CH₂Cl₂ and saturated NaHCO₃. The organic layer was washed with 0.1N HCl, saturated NaCl, dried (MgSO₄), filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (10% MeOH/CH₂Cl₂) affording the unreacted 17 (17 mg, 26%) and diethyl phosphonate 20 (24.5 mg, 41%). ^{1}H NMR (CDCl₃) δ

20   8.00 (s, 1H), 7.70 (d, 2H), 7.16 (d, 2H), 7.00(d, 2H), 6.88 (d, 2H), 5.66 (d, 1H), 4.98-5.10 (m, 2H), 4.39 (m, 1H), 4.24 (m, 5H), 3.89 (s, 3H), 3.602-3.98 (m, 7H), 2.55-3.16 (m, 8H), 1.50-2.00 (m, 7H), 1.36 (t, 6H), 1.08 (m, 2H). ^{31}P NMR (CDCl₃) δ 19.2

Example 19

25   N-methyl pepiridine diethyl phosphonate 21: A solution of compound 20 (22.2 mg, 0.0278 mmol) in THF (1.5 mL) at 0°C was treated with a solution of borane in THF (1M, 0.083 mL). The mixture was stirred for 2 h at room temperature and the starting material was consumed completely as monitored by TLC. The reaction mixture was cooled in an ice/water bath and excess methanol (1 mL) was added to quench the reaction. The solution was concentrated in

30   vacuo and the crude product was chromatographed on silica gel with MeOH/EtOAc to afford compound 21 (7 mg, 32%). ^{1}H NMR (CDCl₃) δ 7.70 (d, 2H), 7.16 (d, 2H), 7.00(d, 2H), 6.88

(d, 2H), 5.66 (d, 1H), 4.98-5.10 (m, 2H), 4.24 (m, 4H), 3.89 (s, 3H), 3.602-3.98 (m, 7H), 2.62-3.15 (m, 9H), 2.26 (s, 3H), 1.52-2.15 (m, 10H), 1.36 (t, 6H). ^{31}P NMR (CDCl$_3$) δ 19.3

Example Section G

Example 1

Compound 1: To a solution of 4-nitrobenzyl bromide (21.6 g, 100 mmol) in toluene (100

5   mL) was added triethyl phosphite (17.15 mL, 100 mL). The mixture was heated at 120°C for

14 hrs. The evaporation under reduced pressure gave a brown oil, which was purified by

flash column chromatography (hexane/EtOAc= 2/1 to 100 % EtOAc) to afford compound 1.

Example 2

10   Compound 2: To a solution of compound 1 (1.0 g) in ethanol (60 mL) was added 10% Pd-C

(300 mg). The mixture was hydrogenated for 14 hrs. Celite was added and the mixture was

stirred for 5 mins. The mixture was filtered through a pad of celite, and washed with ethanol.

Concentration gave compound 2.

15   Example 3

Compound 3: To a solution of compound 3 (292 mg, 1.2 mmol) and aldehyde (111 mg, 0.2

mmol) in methanol (3 mL) was added acetic acid (48 µL, 0.8 mmol). The mixture was

stirred for 5 mins, and sodium cyanoborohydride (25 mg, 0.4 mmol) was added. The mixture

was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added,

20   and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x),

water (2x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column

chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 3.

Example 4

25   Compound 4: To a solution of compound 3 (79 mg , 0.1 mmol) in CH_2Cl_2 (5 mL) was added

trifluoroacetic acid (1 mL). The mixture was stirred for 2 hrs, and solvents were evaporated

under reduced pressure. Coevaporation with EtOAc and CH_2Cl_2 gave an oil. The oil was

dissolved in THF (1mL) and tetrabutylamonium fluoride (0.9 mL, 0.9 mmol) was added. The

mixture was stirred for 1 hr, and solvent was removed. Purification by flash column

30   chromotogaphy (CH_2Cl_2/MeOH = 100/7) gave compound 4.

Example 5

Compound 5: To a solution of compound 4 (0.1 mmol) in acetonitrile (1 mL) at 0°C was

added DMAP (22 mg, 0.18 mmol), followed by bisfurancarbonate (27 mg, 0.09 mmol). The

35   mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed

with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Purification by flash column chromotography (CH_2Cl_2/MeOH = 100/3 to 100/5) afford compound 5 (50 mg): ^{1}H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.9 Hz), 7.11 (2 H, d, J = 8.5 Hz), 6.98 (2 H, d, J = 8.9 Hz), 6.61 (2 H, d, J = 8.5 Hz), 5.71 (1 H, d, J = 5.2 Hz), 5.45 (1 H, m), 5.13 (1 H, m), 4.0 (6 H, m), 3.98-3.70 (4 H, m), 3.86 (3 H, s), 3.38 (2 H, m), 3.22 (1 H, m), 3.02 (5 H, m), 2.8 (1 H, m), 2.0-1.8 (3 H, m), 1.26 (6 H, t, J = 7.0 Hz), 0.95 (3 H, d, J = 6.7 Hz), 0.89 (3 H, d, J = 6.7 Hz).

Example 6

Compound 6: To a solution of compound 5 (30 mg, 0.04 mmol) in MeOH (0.8 mL) was added 37% fomaldehyde (30 μL, 0.4 mmol), followed by acetic acid (23 μL, 0.4 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (25 mg, 0.4 mmol) was added. The reaction mixture was stirred for 14 hrs, and diluted with EtOAc. The organic phase was washed 0.5 N NaOH solution (2x), water (2x), and brine, and dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 6 (11 mg): ^{1}H NMR ($CDCl_3$) δ 7.60 (2 H, d, J = 8.9 Hz), 7.17 (2 H, m), 6.95 (2 H, d, J = 8.9 Hz), 6.77 (2 H, d, J = 8.5 Hz), 5.68 (1 H, d, J = 5.2 Hz), 5.21 (1 H, m), 5.09 (1 H, m), 4.01 (6 H, m), 3.87 (3 H, s), 3.8-3.3 (4 H, m), 3.1-2.6 (7 H, m), 2.90 (3 H, s), 1.8 (3 H, m), 1.25 (6 H, m), 0.91 (6 H, m).

Example 7

Compound 7: To a solution of compound 1 (24.6 g, 89.8 mmol) in acetonitrile (500 mL) was added TMSBr (36 mL, 269 mmol). The reaction mixture was stirred for 14 hrs, and evaporated under reduced pressure. The mixture was coevaporated with MeOH (2x), toluene (2x), EtOAc (2x), and CH_2Cl_2 to give a yellow solid (20 g). To the suspension of above yellow solid (15.8 g, 72.5 mmol) in toluene (140 mL) was added DMF (1.9 mL), followed by thionyl chloride (53 mL, 725 mmol). The reaction mixture was heated at 60°C for 5 hrs, and evaporated under reduced pressure. The mixture was coevaporated with toluene (2x), EtOAc, and CH_2Cl_2 (2x) to afford a brown solid. To the solution of the brown solid in CH_2Cl_2 at 0°C was added benzyl alcohol (29 mL, 290 mmol), followed by slow addition of pyridine (35 mL, 435 mmol). The reaction mixture was allowed to warm to 25°C and stirred for 14 hrs. Solvents were removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over $MgSO_4$. Concentration

gave a dark oil, which was purified by flash column chromatography (hexanes/EtOAc = 2/1 to 1/1) to afford compound 7.

Example 8

5   Compound 8: To a solution of compound 7 (15.3 g) in acetic acid (190 mL) was added Zinc dust (20 g). The mixture was stirred for 14 hrs, and celite was added. The suspension was filtered through a pad of celite, and washed with EtOAc. The solution was concentrated under reduced pressure to dryness. The mixture was diluted with EtOAc, and was washed with 2N NaOH (2x), water (2x), and brine (1x), and dried over $MgSO_4$. Concentration under

10   reduced pressure gave compound 8 as an oil (15 g).

Example 9

Compound 9: To a solution of compound 8 (13.5 g, 36.8 mmol) and aldehyde (3.9 g, 7.0 mmol) in methanol (105 mL) was added acetic acid (1.68 mL, 28 mmol). The mixture was

15   stirred for 5 mins, and sodium cyanoborohydride (882 mg, 14 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH solution (1x), water (2x), and brine (1x), and was dried over $MgSO_4$. Purification by flash column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 9 (6.0 g).

20

Example 10

Compound 10: To a solution of compound 9 (6.2 g , 6.8 mmol) in CH_2Cl_2 (100 mL) was added trifluoroacetic acid (20 mL). The mixture was stirred for 2 hrs, and solvents were evaporated under reduced pressure. Coevaporation with EtOAc and CH_2Cl_2 gave an oil. The

25   oil was dissolved in THF (1mL) and tetrabutylamonium fluoride (0.9 mL, 0.9 mmol) was added. The mixture was stirred for 1 hr, and solvent was removed. Purification by flash column chromotogaphy (CH_2Cl_2/MeOH = 100/7) gave compound 10.

Example 11

30   Compound 11: To a solution of compound 10 (5.6 mmol) in acetonitrile (60 mL) at 0°C was added DMAP (1.36g, 11.1 mmol), followed by bisfurancarbonate (1.65 g, 5.6 mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over $MgSO_4$.

Purification by flash column chromotography (CH₂Cl₂/MeOH = 100/3 to 100/5) afford

compound 11 (3.6 g): ¹H NMR (CDCl₃) δ 7.70 (2 H, d, J = 8.9 Hz), 7.30 (10 H, m), 7.07 (2

H, m), 6.97 (2 H, d, J = 8.9 Hz), 6.58 (2 H, d, J = 8.2 Hz), 5.70 (1 H, d, J = 5.2 Hz), 5.42 (1

H, m), 5.12 (1 H, m), 4.91 (4 H, m), 4.0-3.7 (6 H, m), 3.85 (3 H, s), 3.4 (2 H, m), 3.25 (1 H,

5   m), 3.06 (2 H, d, J = 21 Hz), 3.0 (3 H, m), 2.8 (1 H, m), 1.95 (1 H, m), 1.82 (2 H, m), 0.91 (6

H, m).

Example 12

Compound 12: To a solution of compound 11 (3.6 g) in ethanol (175 mL) was added 10%

10   Pd-C (1.5 g). The reaction mixture was hydrogenated for 14 hrs. The mixture was stirred

with celite for 5 mins, and filtered through a pad of celite. Concentration under reduced

pressure gave compound 12 as a white solid (2.8 g): ¹H NMR (DMSO-d₆) δ 7.68 (2 H, m),

7.08 (2 H, m), 6.93 (2 H, m), 6.48 (2 H, m), 5.95 (1 H, m), 5.0 (2 H, m), 3.9-3.6 (6 H, m),

3.82 (3 H, s), 3.25 (3 H, m), 3.05 (4 H, m), 2.72 (2 H, d, J = 20.1 Hz), 2.0-1.6 (3 H, m), 0.81

15   (6 H, m).

Example 13

Compound 13: Compound 12 (2.6 g, 3.9 mmol) and L-alanine ethyl ester hydrochloride

(3.575 g, 23 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in

20   pyridine (20 mL) and diisopropylethylamine (4.1 mL, 23 mmol) was added. To above

mixture was added a solution of Aldrithiol (3.46 g, 15.6 mmol) and triphenylphosphine (4.08

g, 15.6 g) in pyridine (20 mL). The reaction mixture was stirred for 20 hrs, and solvents were

evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was

washed with 0.5 N NaOH solution (2x), water (2x), and brine, and dried over MgSO₄.

25   Concentration under reduced pressure gave a yellow oil, which was purified by flash column

chromatography (CH₂Cl₂/MeOH = 100/5 to100/10) to afford compound 13 (750 mg): ¹H

NMR (CDCl₃) δ 7.71 (2 H, d, J = 8.8 Hz), 7.13 (2 H, m), 6.98 (2 H, d, J = 8.8 Hz), 6.61 (2 H,

d, J = 8.0 Hz), 5.71 (1 H, d, J = 5.2 Hz), 5.54 (1 H, m), 5.16 (1 H, m), 4.15 (6 H, m), 4.1-3.6

(6 H, m), 3.86 (3 H, s), 3.4-3.2 (3 H, m), 3.1-2.8 (8 H, m), 2.0 (1 H, m), 1.82 (2 H, m), 1.3 (12

30   H, m), 0.92 (6 H, m).

Example 14

Compound 14: To a solution of 4-hydroxypiperidine (19.5 g, 193 mmol) in THF at 0°C was

added sodium hydroxide solution (160 mL, 8.10 g, 203 mmol), followed by di-tert-butyl dicarbonate (42.1 g, 193 mmol). The mixture was warmed to 25°C, and stirred for 12 hours. THF was removed under reduced pressure, and the aqueous phase was extracted with EtOAc (2x). The combined organic layer was washed with water (2x) and brine, and dried over

5   MgSO4. Concentration gave a compound 14 as a white solid (35 g).

Example 15

Compound 15: To a solution of alcohol 14 (5.25 g, 25 mmol) in THF (100 mL) was added sodium hydride (1.2 g, 30 mmol, 60%). The suspension was stirred for 30 mins, and

10   chloromethyl methyl sulfide (2.3 mL, 27.5 mmol) was added. Starting material alcohol 14 still existed after 12 hrs. Dimethy sulfoxide (50 mL) and additional chloromethyl methyl sulfide (2.3 mL, 27.5 mmol) were added. The mixture was stirred for additional 3 hrs, and THF was removed under reduced pressure. The reaction was quenched with water, and extracted with ethyl acetate. The organic phase was washed with water and brine, and was

15   dried over MgSO4. Purification by flash column chromatography (hexanes/EtOAc = 8/1) gave compound 15 (1.24 g).

Example 16

Compound 16: To a solution of compound 15 (693 mg, 2.7 mmol) in CH_2Cl_2 (50 mL) at −

20   78°C was added a solution of sulfuryl chloride (214 μL, 2.7 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was kept at −78°C for 3 hrs, and solvents were removed to give a white solid. The white solid was dissolved in toluene (7 mL), and triethyl phosphite (4.5 mL, 26.6 mmol) was added. The reaction mixture was heated at 120°C for 12 hrs. Solvent and excess reagent was removed under reduced pressure to give compound 16.

25

Example 17

Compound 17: To a solution of compound 17 (600 mg) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 2 hrs, and was concentrated under reduced pressure to give an oil. The oil was diluted with methylene chloride and base resin

30   was added. The suspension was filtered and the organic phase was concentrated to give compound 17.

Example 18

Compound 18: To a solution of compound 17 (350 mg, 1.4 mmol) and aldehyde (100 mg,

0.2 mmol) in methanol (4 mL) was added acetic acid (156 μL, 2.6 mmol). The mixture was

stirred for 5 mins, and sodium cyanoborohydride (164 mg, 2.6 mmol) was added. The

mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water

5   was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH

solution (1x), water (2x), and brine (1x), and was dried over $MgSO_4$. Purification by flash

column chromatography (CH_2Cl_2/MeOH = 100/3) gave compound 18 (62 mg).

Example 19

10   Compound 19: To a solution of compound 18 (62 mg, 0.08 mmol) in THF (3 mL) were

added acetic acid (9 μL, 0.15 mmol) and tetrabutylamonium fluoride (0.45 mL, 1.0 N,

0.45mmol). The mixture was stirred for 3 hr, and solvent was removed. Purification by flash

column chromotogaphy (CH_2Cl_2/MeOH = 100/5) gave an oil. To a solution of above oil in

CH_2Cl_2 (2 mL) was added trifluoroacetic acid (2 mL). The mixture was stirred for 1 hrs, and

15   was concentrated under reduced pressure. Coevaporation with EtOAc and CH_2Cl_2 gave

compound 19.

Example 20

Compound 20: To a solution of compound 19 (55 mg 0.08 mmol) in acetonitrile (1 mL) at

20   0°C was added DMAP (20 mg, 0.16 mmol), followed by bisfurancarbonate (24 mg, 0.08

mmol). The mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase

was washed with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over

$MgSO_4$. Purification by flash column chromotography (CH_2Cl_2/MeOH = 100/3 to 100/5)

afford compound 20 (46 mg): ^{1}H NMR ($CDCl_3$) δ 7.70 (2 H, d, J = 8.9 Hz), 7.01 (2 H, d, J =

25   8.9 Hz), 5.73 (1 H, d, J = 5.1 Hz), 5.51 (1 H, m), 5.14 (1 H, m), 4.16 (1 H, m), 4.06 (1 H, m),

3.94 (3 H, m), 3.86 (3 H, s), 3.80 (1 H, m), 3.75 (2 H, d, J = 9.1 Hz), 3.58 (1 H, m), 3.47 (1 H,

m), 3.30 (1 H, m), 3.1-2.6 (8 H, m), 2.3 (2 H, m), 2.1-1.8 (5 H, m), 1.40 (2 H, m), 1.36 (6 H,

t, J = 7.0 Hz), 0.93 (3 H, d, J = 6.7 Hz), 0.86 (3 h, d, J = 6.7 Hz).

30   Example 21

Compound 21: Compound 21 was made from Boc-4-Nitro-L-Phenylalanine (Fluka)

following the procedure for Compound 2 in Scheme Section A, Scheme 1.

Example 22

Compound 22: To a solution of chloroketone 21 (2.76 g, 8 mmol) in THF (50 mL) and water (6 mL) at 0°C (internal temperature) was added solid NaBH$_4$ (766 mg, 20 mmol) in several portions over a period of 15 min while maintaining the internal temperature below 5°C. The

5   mixture was stirred for 1.5 hrs at 0°C and solvent was removed under reduced pressure. The mixture was quenched with saturated KHSO$_3$ and extracted with EtOAc. The organic phase was washed with waster and brine, and dried overMgSO$_4$. Concentration gave a solid, which was recrystalized from EtOAc/hexane (1/1) to afford the chloroalcohol 22 (1.72 g).

10   Example 23

Compound 23: To a suspension of chloroalcohol 22 (1.8 g, 5.2 mmol) in EtOH (50 mL) was added a solution of KOH in ethanol (8.8 mL, 0.71 N, 6.2 mmol). The mixture was stirred for 2 h at room temperature and ethanol was removed under reduced pressure. The reaction mixture was diluted with EtOAc, and washed with water (2x), saturated NH$_4$Cl (2x), water,

15   and brine, and dried over MgSO$_4$. Concentration under reduced pressure afforded epoxide 23 (1.57g) as a white crystalline solid.

Example 24

Compound 24: To a solution of epoxide 23 (20 g, 65 mmol) in 2-propanol (250 mL) was

20   added isobutylamine (65 mL) and the solution was refluxed for 90 min. The reaction mixture was concentrated under reduced pressure and was coevaporated with MeOH, CH$_3$CN, and CH$_2$Cl$_2$ to give a white solid. To a solution of the white solid in CH$_2$Cl$_2$ (300 mL) at 0°C was added triethylamine (19 mL, 136 mmol), followed by the addition of 4-methoxybenzenesulfonyl chloride (14.1 g, 65 mmol) in CH$_2$Cl$_2$ (50 mL). The reaction

25   mixture was stirred at 0°C for 30 min, and warmed to room temperature and stirred for additional 2 hrs. The reaction solution was concentrated under reduced pressure and was diluted with EtOAc. The organic phase was washed with saturated NaHCO$_3$, water and brine, and dried over MgSO$_4$. Concentration under reduced pressure gave compound 24 as a white solid (37.5 g).

30

Example 25

Compound 25: To a solution of compound 24 (37.5 g, 68 mmol) in CH$_2$Cl$_2$ (100 mL) at 0°C was added a solution of tribromoborane in CH$_2$Cl$_2$ (340 mL, 1.0 N, 340 mmol). The reaction

mixture was kept at 0°C for 1 hr, and warmed to room temperature and stirred for additional

3 hrs. The mixture was cooled to 0°C, and methanol (200 mL) was added slowly. The

mixture was stirred for 1 hr and solvents were removed under reduced pressure to give a

brown oil. The brown oil was coevaporated with EtOAc and toluene to afford compound 25

5   as a brown solid, which was dried under vacuum for 48 hrs.

Example 26

Compound 26: To a solution of compound 25 in THF (80 mL) was added a saturated sodium

bicarbonate solution (25 mL), followed by a solution of Boc2O (982 mg, 4.5 mmol) in THF

10 (20 mL). The reaction mixture was stirred for 5 hrs. THF was removed under reduced

pressure, and aqueous phase was extracted with EtOAc. The organic phase was washed with

water (2x) and Brine (1x), and dried over MgSO$_4$. Purification by flash column

chromatography (hexanes/EtOAc = 1/1) gave compound 26 (467 mg).

15 Example 27

Compound 27: To a solution of compound 26 (300 mg, 0.56 mmol) in THF (6 mL) was

added Cs$_2$CO$_3$ (546 mg, 1.68 mmol), followed by a solution of triflate (420 mg, 1.39 mmol)

in THF (2 mL). The reaction mixture was stirred for 1.5 hrs. The mixture was diluted with

EtOAc, and washed with water (3x) and brine (1x), and dried over MgSO$_4$. Purification by

20 flash column chromatography (hexanes/EtOAc = 1/1 to 1/3) gave compound 27 (300 mg).

Example 28

Compound 28: To a solution of compound 27 (300 mg, 0.38 mmol) in CH$_2$Cl$_2$ (2 mL) was

added trifluoroacetic acid (2 mL). The mixture was stirred for 2.5 hrs, and was concentrated

25 under reduced pressure. The mixture was diluted with EtOAc and was washed with 0.5 N

NaOH solution (3x), water (2x), and brine (1x), and dried over MgSO$_4$. Concentration gave a

white solid. To the solution of above white solid in acetonitrile (3 mL) at 0°C was added

DMAP (93 mg, 0.76 mmol), followed by bisfurancarbonate (112 mg, 0.38 mmol). The

mixture was stirred for 3 hrs at 0°C, and diluted with EtOAc. The organic phase was washed

30 with 0.5 N NaOH solution (2x), water (2x), and brine (1x), and dried over MgSO$_4$.

Purification by flash column chromotography (CH$_2$Cl$_2$/MeOH = 100/3 to 100/5) afford

compound 28 (230 mg): ^{1}H NMR (CDCl$_3$) δ 8.16 (2 H, d, J = 8.5 Hz), 7.73 (2 H, d, J = 9.2

Hz), 7.42 (2 H, d, J = 8.5 Hz), 7.10 (2 H, d, J = 9.2 Hz), 5.65 (1 H,d, J = 4.8 Hz), 5.0 (2 H,

m), 4.34 (2 H, d, J = 10 Hz), 4.25 (4 H, m), 4.0-3.6 (6 H, m), 3.2-2.8 (7 H, m), 1.82 (1 H, m), 1.6 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.95 (6 H, m).

Example 29

5   Compound 29: To a solution of compound 28 (50 mg) in ethanol (5 mL) was added 10% Pd-C (20 mg). The mixture was hydrogenated for 5 hrs. Celite was added, and the mixture was stirred for 5 mins. The reaction mixture was filtered through a pad of celite. Concentration under reduced pressure gave compound 29 (50 mg): ^{1}H NMR (CDCl$_3$) δ 7.72 (2 H, d, J = 8.8 Hz), 7.07 (2 H, 2 H, d, J = 8.8 Hz), 7.00 (2 H, d, J = 8.5 Hz), 6.61 (2 H, d, J = 8.5 Hz), 5.67 (1

10   H, d, J = 5.2 Hz), 5.05 (1 H, m), 4.90 (1 H, m), 4.34 (2 H, d, J = 10.3 Hz), 4.26 (2 H, m), 4.0-3.7 (6 H, m), 3.17 (1 H, m), 2.95 (4 H, m), 2.75 (2 H, m), 1.82 (1 H, m), 1.65 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.93 (3 h, d, J = 6.4 Hz), 0.87 (3 h, d, J = 6.4 Hz).

Example 30

15   Compound 30: To a solution of compound 29 (50 mg, 0.07 mmol) and formaldehyde (52 μL, 37%, 0.7 mmol) in methanol (1 mL) was added acetic acid (40 μL, 0.7 mmol). The mixture was stirred for 5 mins, and sodium cyanoborohydride (44 mg, 0.7 mmol) was added. The mixture was stirred for 14 hrs, and methanol was removed under reduced pressure. Water was added, and was extracted with EtOAc. The organic phase was washed 0.5 N NaOH

20   solution (1x), water (2x), and brine (1x), and was dried over MgSO$_4$. Purification by flash column chromatography (CH$_2$Cl$_2$/MeOH = 100/3) gave compound 30 (40 mg): ^{1}H NMR (CDCl$_3$) δ 7.73 (2 H, d, J = 8.9 Hz), 7.10 (4 H, m), 6.66 (2 H, d, J = 8.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.02 (1 H, m), 4.88 (1 H, m), 4.32 (2 H, d, J = 10.1 Hz), 4.26 (4 H, m), 3.98 (1 H, m), 3.85 (3 H, m), 3.75 (2 H, m), 3.19 (1 H, m), 2.98 (4 H, m), 2.93 (6 H, s), 2.80 (2 H, m),

25   1.82 (1 H, m), 1.62 (2 H, m), 1.39 (6 H, t, J = 7.0 Hz), 0.90 (6 H, m).

Example 31

Compound 31: To a suspension of compound 25 (2.55 g, 5 mmol) in CH$_2$Cl$_2$ (20 mL) at 0°C was added triehtylamine (2.8 mL, 20 mmol), followed by TMSCl (1.26 mL, 10 mmol). The

30   mixture was stirred at 0°C for 30 mins, and warmed to 25°C and stirred for additional 1 hr. Concentration gave a yellow solid. The yellow solid was dissolved in acetonitrile (30 mL) and cooled to 0°C. To this solution was added DMAP (1.22 g, 10 mmol) and Bisfurancarbonate (1.48 g, 5 mmol). The reaction mixture was stirred at 0°C for 2 hrs and for

additional 1 hr at 25°C. Acetonitrile was removed under reduced pressure. The mixture was diluted with EtOAc, and washed with 5% citric acid (2x), water (2x), and brine (1x), and dried over MgSO₄. Concentration gave a yellow solid. The yellow solid was dissolved in THF (40 mL), and acetic acid (1.3 mL, 20 mmol) and tetrabutylammonium fluoride (8mL,

5   1.0 N, 8mmol) were added. The mixture was stirred for 20 mins, and THF was removed under reduced pressure. Purification by flash column chromatography (hexenes/EtOAc = 1/1) gave compound 31 (1.5 g).

Example 32

10 Compound 32: To a solution of compound 31 (3.04 g, 5.1 mmol) in THF (75 mL) was added Cs₂CO₃ (3.31 g, 10.2 mmol), followed by a solution of triflate (3.24 g, 7.65 mmol) in THF (2 mL). The reaction mixture was stirred for 1.5 hrs, and THF was removed under reduced pressure. The mixture was diluted with EtOAc, and washed with water (3x) and brine (1x), and dried over MgSO₄. Purification by flash column chromatography (hexanes/EtOAc = 1/1

15 to 1/3) gave compound 32 (2.4 g): ¹H NMR (CDCl₃) δ 8.17 (2 H, d, J = 8.5 Hz), 7.70 (2 H, J = 9.2 Hz), 7.43 (2 H, d, J = 8.5 Hz), 7.37 (10 H, m), 6.99 (2 H, d, J =9.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.15 (4 H, m), 5.05 (2 H, m), 4.26 (2 H, d, J = 10.2 Hz), 3.9-3.8 (4 H, m), 3.75 (2 H, m), 3.2-2.8 (7 H, m), 1.82 (1 H, m), 1.62 (2 H, m), 0.92 (6 H, m).

20 Example 33

Compound 33: To a solution of compound 32 (45 mg) in acetic acid (3 mL) was added zinc (200 mg). The mixture was stirred for 5 hrs. Celite was added, and the mixture was filtered and washed with EtOAc. The solution was concentrated to dryness and diluted with EtOAc. The organic phase was washed with 0.5 N NaOH solution, water, and brine, and dried over

25 MgSO₄. Purification by flash column chromatography (CH₂Cl₂/isoproanol = 100/5) gave compound 33 (25 mg): ¹H NMR (CDCl₃) δ 7.67 (2 H, d, J = 8.8 Hz), 7.36 (10 H, m), 6.98 (4 H, m), 6.60 (2 H, d, J = 8.0 Hz), 5.67 (1 H, d, J = 4.9 Hz), 5.12 (4 H, m), 5.05 (1 H, m), 4.90 (1 H, m), 4.24 (2 H, d, J = 10.4 Hz), 4.0-3.6 (6 H, m), 3.12 (1 H, m), 3.95 (4 H, m), 2.75 (2 H, m), 1.80 (1 H, m), 1.2 (2 H, m), 0.9 (6 H, m).

30

Example 34

Compound 34: To a solution of compound 32 (2.4 g) in ethanol (140 mL) was added 10% Pd-C (1.0 g). The mixture was hydrogenated for 14 hrs. Celite was added, and the mixture

was stirred for 5 mins. The slurry was filtered through a pad of celite, and washed with pyridine. Concentration under reduced pressure gave compound 34: ^{1}H NMR (DMSO-d$_6$) δ 7.67 (2 H, d, J = 8.9 Hz), 7.14 (2 H, d, J = 8.9 Hz), 6.83 (2 H, d, J = 8.0 Hz), 6.41 (2 H, d, J = 8.0 Hz), 5.51 (1 H, d, J = 5.2 Hz), 5.0-4.8 (2 H, m), 4.15 (2 H, d, J = 10.0 Hz), 3.9-3.2 (8 H,
5   m), 3.0 (2 H, m), 2.8 (4 H, m), 2.25 (1 H, m), 1.4 (2 H, m), 0.8 (6 H, m).

Example 35

Compound 35: Compound 34 (1.62 g, 2.47 mmol) and L-alanine butyl ester hydrochloride (2.69 g, 14.8 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in
10   pyridine (12 mL) and diisopropylethylamine (2.6 mL, 14.8 mmol) was added. To above mixture was added a solution of Aldrithiol (3.29 g, 14.8 mmol) and triphenylphosphine (3.88 g, 14.8 g) in pyridine (12 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with 0.5 N NaOH solution (2x), water (2x), and brine, and dried over MgSO$_4$.
15   Concentration under reduced pressure gave a yellow oil, which was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH = 100/5 to100/15) to afford compound 35 (1.17 g): ^{1}H NMR (CDCl$_3$) δ 7.70 (2 H, d, J = 8.6 Hz), 7.05 (2 H, d, J =8.6 Hz), 6.99 (2 H, d, J = 8.0 Hz), 6.61 (2 H, d, J = 8.0 Hz), 5.67 (1 H, d, J = 5.2 Hz), 5.05 (1 H, m), 4.96 (1 H, m), 4.28 (2 H, m), 4.10 (6 H, m), 4.0-3.6 (6 H, m), 3.12 (2 H, m), 2.92 (3 H, m), 2.72 (2 H, m), 1.82 (1 H,
20   m), 1.75-1.65 (2 H, m), 1.60 (4 H, m), 1.43 (6 H, m), 1.35 (4 H, m), 0.91 (12 H, m).

Example 36

Compound 37: Compound 36 (100 mg, 0.15 mmol) and L-alanine butyl ester hydrochloride (109 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in
25   pyridine (1 mL) and diisopropylethylamine (105 μL, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over MgSO$_4$. Concentration under reduced
30   pressure gave an oil, which was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH = 100/5 to100/15) to afford compound 37 (21 mg): ^{1}H NMR (CDCl$_3$) δ 7.71 (2 H, d, J = 8.8 Hz), 7.15 (2 H, d, J = 8.2 Hz), 7.01 (2 H, d, J = 8.8 Hz), 6.87 (2 H, d, J = 8.2 Hz), 5.66 (1 H, d, J = 5.2 Hz), 5.03 (1 H, m), 4.95 (1 H, m),4.2-4.0 (8 H, m), 3.98 (1 H, m), 3.89 (3 H, s),

3.88-3.65 (5 H, m), 3.15 (1 H, m), 2.98 (4 H, m), 2.82 (2 H, m), 1.83 (1 H, m), 1.63 (4 H, m), 1.42 (6 H, m), 1.35 (4 H, m), 0.95 (12 H, m).

Example 37

5   Compound 38: Compound 36 (100 mg, 0.15 mmol) and L-leucine ethyl ester hydrochloride (117 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (105 μL, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents

10   were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/15) to afford compound 38 (12 mg): ^1H NMR (CDCl$_3$) δ 7.72 (2 H, d, J = 8.5 Hz), 7.14 (2 H, d, J = 8.0 Hz), 7.00 (2 H, d, J = 8.5 Hz), 6.86 (2 H, d, J = 8.0 Hz), 5.66 (1 H,

15   d, J = 5.2 Hz), 5.05 (1 H, m), 4.95 (1 H, m), 4.2-4.0 (8 H, m), 4.0-3.68 (6 H, m), 3.88 (3 H, s), 3.2-2.9 (5 H, m), 2.80 (2 H, m), 1.80 (1 H, m), 1.65 (4 H, m), 1.65-1.50 (4 H, m), 1.24 (6 H, m), 0.94 (18 H, m).

Example 38

20   Compound 39: Compound 36 (100 mg, 0.15 mmol) and L-leucine butyl ester hydrochloride (117 mg, 0.60 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in pyridine (1 mL) and diisopropylethylamine (105 μL, 0.6 mmol) was added. To above mixture was added a solution of Aldrithiol (100 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in pyridine (1 mL). The reaction mixture was stirred for 20 hrs, and solvents

25   were evaporated under reduced pressure. The mixture was diluted with ethyl acetate, and was washed with water (2x), and brine, and dried over $MgSO_4$. Concentration under reduced pressure gave an oil, which was purified by flash column chromatography (CH_2Cl_2/MeOH = 100/5 to100/15) to afford compound 39 (32 mg): ^1H NMR (CDCl$_3$) δ 7.72 (2 H, d, J = 8.8 Hz), 7.15 (2 H, d, J = 8.0 Hz), 7.0 (2 H, d, J = 8.8 Hz), 6.89 (2 H, d, J = 8.0 Hz), 5.66 (1 H, d,

30   J = 4.3 Hz), 5.07 (1 H, m), 4.94 (1 H, m), 4.2-4.0 (8 H, m), 3.89 (3 H, s), 4.0-3.6 (6 H, m), 3.2-2.9 (5 H, m), 2.8 (2 H, m), 1.81 (1 H, m), 1.78-1.44 (10 H, m), 1.35 (4 H, m), 0.95 (24 H, m).

Example 39

Compound 41: Compound 40 (82 mg, 0.1 mmol) and L-alanine isopropyl ester
hydrochloride (92 mg, 0.53 mmol) were coevaporated with pyridine (2x). The mixture was
dissolved in pyridine (1 mL) and diisopropylethylamine (136 μL, 0.78 mmol) was added. To

5   above mixture was added a solution of Aldrithiol (72 mg, 0.33 mmol) and triphenylphosphine
(87 mg, 0.33 mmol) in pyridine (1 mL). The reaction mixture was stirred at 75°C for 20 hrs,
and solvents were evaporated under reduced pressure. The mixture was diluted with ethyl
acetate, and was washed with water (2x), and brine, and dried over MgSO₄. Concentration
under reduced pressure gave an oil, which was purified by flash column chromatography

10 (CH₂Cl₂/MeOH = 100/1 to100/3) to afford compound 41 (19 mg): ^{1}H NMR (CDCl₃) δ 7.71
(2 H, d, J = 8.9 Hz), 7.2-7.35 (5 H, m), 7.15 (2 H, m), 7.01 (2 H, d, J = 8.9 Hz), 6.87 (2 H, m),
5.65 (1 H, d, J = 5.4 Hz), 5.05-4.93 (2 H, m), 4.3 (2 H, m), 4.19 (1 H, m), 3.98 (1 H, m), 3.88
(3 H, s), 3.80 (2 H, m), 3.70 (3 H, m), 3.18 (1 H, m), 2.95 (4 H, m), 2.78 (2 H, m), 1.82 (1 H,
m), 1.62 (2 H, m), 1.35 (3 H, m), 1.25-1.17 (6 H, m), 0.93 (3 H, d, J = 6.4 Hz), 0.88 (3 H, d, J

15 = 6.4 Hz).

Example 40

Compound 42: Compound 40 (100 mg, 0.13 mmol) and L-glycine butyl ester hydrochloride
(88 mg, 0.53 mmol) were coevaporated with pyridine (2x). The mixture was dissolved in

20 pyridine (1 mL) and diisopropylethylamine (136 μL, 0.78 mmol) was added. To above
mixture was added a solution of Aldrithiol (72 mg, 0.33 mmol) and triphenylphosphine (87
mg, 0.33 mmol) in pyridine (1 mL). The reaction mixture was stirred at 75°C for 20 hrs, and
solvents were evaporated under reduced pressure. The mixture was diluted with ethyl
acetate, and was washed with water (2x), and brine, and dried over MgSO₄. Concentration

25 under reduced pressure gave an oil, which was purified by flash column chromatography
(CH₂Cl₂/MeOH = 100/1 to100/3) to afford compound 42 (18 mg): ^{1}H NMR (CDCl₃) δ 7.71
(2 H, d, J = 9.2 Hz), 7.35-7.24 (5 H, m), 7.14 (2 H, m), 7.00 (2 H, d, J = 8.8 Hz), 6.87 (2 H,
m), 5.65 (1 H, d, J = 5.2 Hz), 5.04 (1 H, m), 4.92 (1 H, m), 4.36 (2 H, m), 4.08 (2 H, m), 3.95
(3 H, m), 3.88 (3 H, s), 3.80 (2 H, m), 3.76 (3 H, m), 3.54 (1 H, m), 3.15 (1 H, m), 2.97 (4 H,

30 m), 2.80 (2 H, m), 1.82 (1 H, m), 1.62 (4 H, m), 1.35 (2 H, m), 0.9 (9 H, m).

Example Section H

Example 1

Sulfonamide 1: To a suspension of epoxide (20 g, 54.13 mmol) in 2-propanol (250 mL) was

5   added isobutylamine (54 mL, 541 mmol) and the solution was refluxed for 30 min. The

solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2

(250 mL) and cooled to 0°C. Triethylamine (15.1 mL, 108.26 mmol) was added followed by

the addition of 4-nitrobenzenesulfonyl chloride (12 g, 54.13 mmol) and the solution was

stirred for 40 min at 0°C, warmed to room temperature for 2 h, and evaporated under reduced

10   pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic

phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under

reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the

sulfonamide (30.59 g, 90%) as an off-white solid.

15   **Example 2**

Phenol 2: A solution of sulfonamide 1 (15.58 g, 24.82 mmol) in EtOH (450 mL) and CH_2Cl_2

(60 mL) was treated with 10% Pd/C (6 g). The suspension was stirred under H_2 atmosphere

(balloon) at room temperature for 24 h. The reaction mixture was filtered through a plug of

celite and concentrated under reduced pressure. The crude product was purified by column

20   chromatography on silica gel (6% $MeOH/CH_2Cl_2$) to give the phenol (11.34 g, 90%) as a

white solid.

Example 3

Dibenzylphosphonate 3: To a solution of phenol 2 (18.25 g, 35.95 mmol) in CH_3CN (200

25   mL) was added Cs_2CO_3 (23.43 g, 71.90 mmol) and triflate (19.83 g, 46.74 mmol). The

reaction mixture was stirred at room temperature for 1 h and the solvent was evaporated

under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl.

The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure.

The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane)

30   to give the dibenzylphosphonate (16.87 g, 60%) as a white solid.

Example 4

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Amine 4: A solution of dibenzylphosphonate (16.87 g, 21.56 mmol) in CH$_2$Cl$_2$ (60 mL) at 0°C was treated with trifluoroacetic acid (30 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH.

5   The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure to give the amine (12.94 g, 88%) as a white solid.

Example 5

10   Carbonate 5: To a solution of (S)-(+)-3-hydroxytetrahydrofuran (5.00 g, 56.75 mmol) in CH$_2$Cl$_2$ (80 mL) was added triethylamine (11.86 mL, 85.12 mmol) and bis(4-nitrophenyl)carbonate (25.90 g, 85.12 mmol). The reaction mixture was stirred at room temperature for 24 h and partitioned between CH$_2$Cl$_2$ and saturated NaHCO$_3$. The CH$_2$Cl$_2$ layer was dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by

15   column chromatography on silica gel (2/1-EtOAc/hexane) to give the carbonate (8.62 g, 60%) as a pale yellow oil which solidified upon refrigerating.

Example 6

Carbamate 6: Two methods have been used.

20   Method 1: To a solution of 4 (6.8 g, 9.97 mmol) and 5 (2.65 g, 10.47 mmol) in CH$_3$CN (70 mL) at 0 °C was added 4-(dimethylamino)pyridine (2.44 g, 19.95 mmol). The reaction mixture was stirred at 0°C for 3 h and concentrated. The residue was dissolved in EtOAc and washed with 0.5 N NaOH, saturated NaHCO$_3$, H$_2$O, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3%

25   2-propanol/CH$_2$Cl$_2$) to give the carbamate (3.97 g, 50%) as a pale yellow solid.

Method 2: To a solution of 4 (6.0 g, 8.80 mmol) and 5 (2.34 g, 9.24 mmol) in CH$_3$CN (60 mL) at 0°C was added 4-(dimethylamino)pyridine (0.22 g, 1.76 mmol) and N, N-diisopropylethylamine (3.07 mL, 17.60 mmol). The reaction mixture was stirred at 0°C for 1

30   h and warmed to room temperature overnight. The solvent was evaporated under reduced pressure. The crude product was dissolved in EtOAc and washed with 0.5 N NaOH, saturated NaHCO$_3$, H$_2$O, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product

was purified by column chromatography on silica gel (3% 2-propanol/CH₂Cl₂) to give the carbamate (3.85 g, 55%) as a pale yellow solid.

Example 7

Phosphonic Acid 7: To a solution of 6 (7.52 g, 9.45 mmol) in MeOH (350 mL) was added 10% Pd/C (3 g). The suspension was stirred under H₂ atmosphere (balloon) at room temperature for 48 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (5.24 g, 90%) as a white solid.

Example 8

Cbz Amide 8: To a solution of 7 (5.23 g, 8.50 mmol) in CH₃CN (50 mL) was added N, O-bis(trimethylsilyl)acetamide (16.54 mL, 68 mmol) and then heated to 70°C for 3 h. The reaction mixture was cooled to room temperature and concentrated. The residue was co-evaporated with toluene and dried under vacuum to afford the silylated intermediate which was used directly without any further purification. To a solution of the silylated intermediate in CH₂Cl₂ (40 mL) at 0°C was added pyridine (1.72 mL, 21.25 mmol) and benzyl chloroformate (1.33 mL, 9.35 mmol). The reaction mixture was stirred at 0°C for 1 h and warmed to room temperature overnight. A solution of MeOH (50 mL) and 1% aqueous HCl (150 mL) was added at 0°C and stirred for 30 min. CH₂Cl₂ was added and two layers were separated. The organic layer was dried with Na₂SO₄, filtered, concentrated, co-evaporated with toluene, and dried under vacuum to give the Cbz amide (4.46 g, 70%) as an off-white solid.

Example 9

Diphenylphosphonate 9: A solution of 8 (4.454 g, 5.94 mmol) and phenol (5.591 g, 59.4 mmol) in pyridine (40 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (4.903 g, 23.76 mmol) was added. The reaction mixture was stirred at 70°C for 4 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off. The filtrate was concentrated and dissolved in CH₃CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated. The crude product was purified by

column chromatography on silica gel (4% 2-propanol/CH$_2$Cl$_2$) to give the diphenylphosphonate (2.947 g, 55%) as a white solid.

Example 10

Monophosphonic Acid 10: To a solution of 9 (2.945 g, 3.27 mmol) in CH$_3$CN (25 mL) at 0°C was added 1N NaOH (8.2 mL, 8.2 mmol). The reaction mixture was stirred at 0°C for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (2.427 g, 90%) as a white solid.

Example 11

Cbz Protected Monophosphoamidate 11: A solution of 10 (2.421 g, 2.93 mmol) and L-alanine isopropyl ester hydrochloride (1.969 g, 11.73 mmol) in pyridine (20 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (3.629 g, 17.58 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H$_2$O, saturated NaHCO$_3$, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH$_2$Cl$_2$) to give the monoamidate (1.569 g, 57%) as a white solid.

Example 12

Monophosphoamidate12: To a solution of 11 (1.569 g, 1.67 mmol) in EtOAc (80 mL) was added 10% Pd/C (0.47 g). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and the crude product was purified by column chromatography on silica gel (CH$_2$Cl$_2$ to 1-8% 2-propanol/CH$_2$Cl$_2$) to give the monophosphoamidate 12a (1.12 g, 83%, **GS 108577**, 1:1 diastereomeric mixture A/B) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.45 (dd, 2H), 7.41-7.17 (m, 7H), 6.88 (dd, 2H), 6.67 (d, J = 8.4 Hz, 2H), 5.16 (broad s, 1H), 4.95 (m, 1H), 4.37-4.22 (m, 5H), 3.82-3.67 (m, 7H), 2.99-2.70 (m, 6H), 2.11-1.69 (m, 3H), 1.38 (m, 3H), 1.19 (m, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.5, 19.6. 12b (29 mg, 2%, **GS108578**, diastereomer A) as a white solid: ^{1}H NMR (CDCl$_3$)

δ 7.43 (d, J = 7.8 Hz, 2H), 7.35-7.17 (m, 7H), 6.89 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 5.16 (broad s, 1H), 4.96 (m, 1H), 4.38-4.32 (m, 4H), 4.20 (m, 1H), 3.82-3.69 (m, 7H), 2.99-2.61 (m, 6H), 2.10 (m, 1H), 1.98 (m, 1H), 1.80 (m, 1H), 1.38 (d, J = 7.2 Hz, 3H), 1.20 (d, J = 6.3 Hz, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.5. 12c (22 mg, 1.6%, **GS 108579**, diastereomer B) as a white solid : ^{1}H NMR (CDCl$_3$) δ 7.45 (d, J = 8.1 Hz, 2H), 7.36-7.20 (m, 7H), 6.87 (d, J = 8.7 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 5.15 (broad s, 1H), 4.95 (m, 1H), 4.34-4.22 (m, 5H), 3.83-3.67 (m, 7H), 2.99-2.64 (m, 6H), 2.11-1.68 (m, 3H), 1.33 (d, J = 6.9 Hz, 3H), 1.20 (d, J = 6.0 Hz, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 19.6.

Example 13

Sulfonamide 13: To a suspension of epoxide (1.67 g, 4.52 mmol) in 2-propanol (25 mL) was added isobutylamine (4.5 mL, 45.2 mmol) and the solution was refluxed for 30 min. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH$_2$Cl$_2$ (20 mL) and cooled to 0°C. Triethylamine (1.26 mL, 9.04 mmol) was added followed by the treatment of 3-nitrobenzenesulfonyl chloride (1.00 g, 4.52 mmol). The solution was stirred for 40 min at 0°C, warmed to room temperature for 2 h, and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaHCO$_3$. The organic phase was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the sulfonamide (1.99 g, 70%) as a white solid.

Example 14

Phenol 14: Sulfonamide 13 (1.50 g, 2.39 mmol) was suspended in HOAc (40 mL) and concentrated HCl (20 mL) and heated to reflux for 3 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was partitioned between 10% MeOH/CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic layers were washed with NaHCO$_3$, H$_2$O, dried with Na$_2$SO$_4$, filtered, and concentrated to give a yellow solid. The crude product was dissolved in CHCl$_3$ (20 mL) and treated with triethylamine (0.9 mL, 6.45 mmol) followed by the addition of Boc$_2$O (0.61 g, 2.79 mmol). The reaction mixture was stirred at room temperature for 6 h. The product was partitioned between CHCl$_3$ and H$_2$O. The CHCl$_3$ layer was washed with NaHCO$_3$, H$_2$O, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1-5%

MeOH/CH2Cl2) to give the phenol (0.52 g, 45%) as a pale yellow solid.

Example 15

Dibenzylphosphonate 15: To a solution of phenol 14 (0.51 g, 0.95 mmol) in CH3CN (8 mL)

5   was added Cs2CO3 (0.77 g, 2.37 mmol) and triflate (0.8 g, 1.90 mmol). The reaction mixture

was stirred at room temperature for 1.5 h and the solvent was evaporated under reduced

pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic

phase was dried Na2SO4, filtered, and evaporated under reduced pressure. The crude product

was purified by column chromatography on silica gel (3% MeOH/CH2Cl2) to give the

10   dibenzylphosphonate (0.62 g, 80%) as a white solid.

Example 16

Amine 16: A solution of dibenzylphosphonate 15 (0.61 g, 0.75 mmol) in CH2Cl2 (8 mL) at

0°C was treated with trifluoroacetic acid (2 mL). The solution was stirred for 30 min at 0°C

15   and then warmed to room temperature for an additional 30 min. Volatiles were evaporated

under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH.

The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried

(Na2SO4), filtered, and evaporated under reduced pressure to give the amine (0.48 g, 90%)

which was used directly without any further purification.

20

Example 17

Carbamate 17: To a solution of amine 16 (0.48 g, 0.67 mmol) in CH3CN (8 mL) at 0°C was

treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (0.2 g,

0.67 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.) and 4-

25   (dimethylamino)pyridine (0.17 g, 1.34 mmol). After stirring for 2 h at 0°C, the reaction

solvent was evaporated under reduced pressure and the residue was partitioned between

EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric

acid (2 x), saturated NaHCO3, dried with Na2SO4, filtered, and evaporated under reduced

pressure. The crude product was purified by column chromatography on silica gel (3% 2-

30   propanol/CH2Cl2) to give the carbamate (0.234 g, 40%) as a white solid.

Example 18

Analine 18: To a solution of carbamate 17 (78 mg, 0.09 mmol) in 2 mL HOAc was added zinc powder. The reaction mixture was stirred at room temperature for 1.5 h and filtered through a small plug of celite. The filtrate was concentrated and co-evaporated with toluene. The crude product was purified by column chromatography on silica gel (5% 2-
5   propanaol/CH_2Cl_2) to give the analine (50 mg, 66%) as a white solid.

Example 19

Phosphonic Acid 19: To a solution of analine (28 mg, 0.033mmol) in MeOH (1 mL) and HOAc (0.5 mL) was added 10% Pd/C (14 mg). The suspension was stirred under H_2
10   atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a small plug of celite. The filtrate was concentrated, co-evaporated with toluene, and dried under vacuum to give the phosphonic acid (15 mg, 68%, GS 17424) as a white solid: ^{1}H NMR (DMSO-d_6) δ 7.16-6.82 (m, 8H), 5.50 (d, 1H), 4.84 (m, 1H), 3.86-3.37 (m, 9H), 2.95-2.40 (m, 6H), 1.98 (m, 1H), 1.42-1.23 (m, 2H), 0.84 (d, J = 6.3 Hz, 3H), 0.79 (d, J = 6.3
15   Hz,3H). MS (ESI) 657 (M-H).

Example 20

Phenol 21: A suspension of aminohydrobromide salt 20 (22.75 g, 44 mmol) in CH_2Cl_2 (200 mL) at 0°C was treated with triethylamine (24.6 mL, 176 mmol) followed by slow addition of
20   chlorotrimethylsilane (11.1 mL, 88 mmol). The reaction mixture was stirred at 0°C for 30 min and warmed to room temperature for 1 h. The solvent was removed under reduced pressure to give a yellow solid. The crude product was dissolved in CH_2Cl_2 (300 mL) and treated with triethylamine (18.4 mL, 132 mmol) and Boc_2O (12 g, 55 mmol). The reaction mixture was stirred at room temperature overnight. The product was partitioned between
25   CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was washed with $NaHCO_3$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was dissolved in THF (200 mL) and treated with 1.0 M TBAF (102 mL, 102 mmol) and HOAc (13 mL). The reaction mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The residue was partitioned between CH_2Cl_2 and H_2O, dried with Na_2SO_4, filtered, and concentrated.
30   The crude product was purified by column chromatography on silica gel (1-3% 2-propanol/CH_2Cl_2) to give the phenol (13.75 g, 58%) as a white solid.

Example 21

Dibenzylphosphonate 22: To a solution of phenol 21 (13.70 g, 25.48 mmol) in THF (200
mL) was added Cs_2CO_3 (16.61 g, 56.96 mmol) and triflate (16.22 g, 38.22 mmol). The
reaction mixture was stirred at room temperature for 1 h and the solvent was evaporated
under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl.

5   The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure.
The crude product was purified by column chromatography on silica gel (3% $MeOH/CH_2Cl_2$)
to give the dibenzylphosphonate (17.59 g, 85%) as a white solid.

Example 22

10   Amine 23: A solution of dibenzylphosphonate 22 (17.58 g, 21.65 mmol) in CH_2Cl_2 (60 mL)
at 0°C was treated with trifluoroacetic acid (30 mL). The solution was stirred for 30 min at
0°C and then warmed to room temperature for an additional 1.5 h. Volatiles were evaporated
under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH.
The organic phase was washed with 0.5 N NaOH (2x), water (2x), saturated NaCl, dried with

15   Na_2SO_4, filtered, and evaporated under reduced pressure to give the amine (14.64 g, 95%)
which was used directly without any further purification.

Example 23

Carbamate 24: To a solution of amine 23 (14.64 g, 20.57 mmol) in CH_3CN (200 mL) at 0°C

20   was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate
(6.07 g, 20.57 mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and
4-(dimethylamino)pyridine (5.03 g, 41.14mmol). After stirring for 2 h at 0°C, the reaction
solvent was evaporated under reduced pressure and the residue was partitioned between
EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric

25   acid (2 x), saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and evaporated under reduced
pressure. The crude product was purified by column chromatography on silica gel (3% 2-
propanol/CH_2Cl_2) to give the carbamate (10 g, 56%) as a white solid.

Example 24

30   Phosphonic Acid 25: To a solution of carbamate 24 (8 g, 9.22 mmol) in EtOH (500 mL was
added 10% Pd/C (4 g). The suspension was stirred under H_2 atmosphere (balloon) at room
temperature for 30 h. The reaction mixture was filtered through a plug of celite. The celite
paste was suspended in pyridine and stirred for 30 min and filtered. This process was

repeated twice. The combined solution was concentrated under reduced pressure to give the phosphonic acid (5.46 g, 90%) as an off-white solid.

Example 25

Cbz Amide 26: To a solution of 25 (5.26 g, 7.99 mmol) in CH_3CN (50 mL) was added N, O-bis(trimethylsilyl)acetamide (15.6 mL, 63.92 mmol) and then heated to 70°C for 3 h. The reaction mixture was cooled to room temperature and concentrated. The residue was co-evaporated with toluene and dried under vacuum to afford the silylated intermediate which was used directly without any further purification. To a solution of the silylated intermediate in CH_2Cl_2 (40 mL) at 0°C was added pyridine (1.49 mL, 18.38 mmol) and benzyl chloroformate (1.25mL, 8.79 mmol). The reaction mixture was stirred at 0°C for 1 h and warmed to room temperature overnight. A solution of MeOH (50 mL) and 1% aqueous HCl (150 mL) was added at 0°C and stirred for 30 min. CH_2Cl_2 was added and two layers were separated. The organic layer was dried with Na_2SO_4, filtered, concentrated, co-evaporated with toluene, and dried under vacuum to give the Cbz amide (4.43 g, 70%) as an off-white solid.

Example 26

Diphenylphosphonate 27: A solution of 26 (4.43 g, 5.59 mmol) and phenol (4.21 g, 44.72 mmol) in pyridine (40 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (4.62 g, 22.36 mmol) was added. The reaction mixture was stirred at 70°C for 36 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off. The filtrate was concentrated and dissolved in CH_3CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane to EtOAc) to give the diphenylphosphonate (2.11 g, 40%) as a pale yellow solid.

Example 27

Monophosphonic Acid 28: To a solution of 27 (2.11 g, 2.24 mmol) in CH_3CN (15 mL) at 0°C was added 1N NaOH (5.59 mL, 5.59 mmol). The reaction mixture was stirred at 0°C for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-

evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (1.75 g, 90%) as a white solid.

Example 28

Cbz Protected Monophosphoamidate 29: A solution of 28 (1.54 g, 1.77 mmol) and L-alanine isopropyl ester hydrochloride (2.38 g, 14.16 mmol) in pyridine (15 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (2.20 g, 10.62 mmol) was added. The reaction mixture was stirred at 70°C overnight and cooled to room temperature. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H_2O, saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the monophosphoamidate (0.70g, 40%) as an off-white solid.

Example 29

Monophosphoamidate 30a-b: To a solution of 29 (0.70 g, 0.71 mmol) in EtOH (10 mL) was added 10% Pd/C (0.3 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a small plug of celite. The filtrate was concentrated and the crude products were purified by column chromatography on silica gel (7-10% MeOH/CH_2Cl_2) to give the monoamidates 30a (0.106 g, 18%, **GS 77369**, 1/1 diastereomeric mixture) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.71 (d, J = 8.7 Hz, 2H), 7.73-7.16 (m, 5H), 7.10-6.98 9m, 4H), 6.61 (d, J = 8.1 Hz, 2H), 5.67 (d, J = 4.8 Hz, 1H), 5.31-4.91 (m, 2H), 4.44 (m, 2H), 4.20 (m, 1H), 4.00-3.61 (m, 6H), 3.18-2.74 (m, 7H), 1.86-1.64 (m, 3H), 1.38 (m, 3H), 1.20 (m, 6H), 0.93 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) □ 19.1, 18; MS(ESI) 869 (M+Na). 30b (0.200 g, 33%, **GS 77425**, 1/1 diastereomeric mixture) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.73 (dd, J = 8.7 Hz, J = 1.5 Hz, 2H), 7.36-7.16 (m, 5H), 7.09-7.00 (m, 4H), 6.53 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.4 Hz, 1H), 5.06-4.91 (m, 2H), 4.40 (m, 2H), 4.20 (m, 1H), 4.00-3.60 (m, 6H), 3.14 (m, 3H), 3.00-2.65 (m, 6H), 1.86-1.60 (m, 3H), 1.35 (m, 3H), 1.20 (m, 9H), 0.92 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31} P NMR (CDCl$_3$) □ 19.0, 17.9. MS (ESI) 897 (M+Na).

Example 30

Synthesis of Bisamidates 32: A solution of phosphonic acid 31 (100 mg, 0.15 mmol) and L-valine ethyl ester hydrochloride (108 mg, 0.60 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph_3P (117 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (98 mg, 0.45 mmol) in pyridine (1 mL) followed by addition of N,N-diisopropylethylamine (0.1 mL, 0.60 mmol). The reaction mixture was stirred at room temperature for two days. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to give the bisamidate (73 mg, 53%, **GS 17389**) as a white solid: ^1H NMR $(CDCl_3)$ δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.1 Hz, 2H), 5.66 (d, J = 4.8 Hz, 1H), 5.05 (m, 1H), 4.95 (d, J = 8.7 Hz, 1H), 4.23-4.00 (m ,4H,), 3.97-3.68 (m, 11H), 3.39-2.77 (m, 9H), 2.16 (m, 2H), 1.82-1.60 (m, 3H), 1.31-1.18 (m, 6H), 1.01-0.87 (m, 18H); ^{31}P NMR $(CDCl_3)$ δ 21.3; MS (ESI) 950 (M+Na).

Example 31

Triflate 34: To a solution of phenol 33 (2.00 g, 3.46 mmol) in THF (15 mL) and CH_2Cl_2 (5 mL) was added N-phenyltrifluoromethanesulfonimide (1.40 g, 3.92 mmol) and cesium carbonate (1.40 g, 3.92 mmol). The reaction mixture was stirred at room temperature overnight and concentrated. The crude product was partitioned between CH_2Cl_2 and saturated NaCl, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% $MeOH/CH_2Cl_2$) to give the triflate (2.09 g, 85%) as a white solid.

Example 32

Aldehyde 35: To a suspension of triflate 34 (1.45 g, 2.05 mmol), palladium (II) acetate (46 mg, 0.20 mmol) and 1,3-bis(diphenylphosphino)propane (84 mg, 0.2 mmol) in DMF (8 mL) under CO atmosphere (balloon) was slowly added triethylamine (1.65 mL, 11.87 mmol) and triethylsilane (1.90 mL, 11.87 mmol). The reaction mixture was heated to 70°C under CO atmosphere (balloon) and stirred overnight. The solvent was concentrated under reduced pressure and partitioned between CH_2Cl_2 and H_2O. The organic phase was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the aldehyde (0.80 g, 66%) as a white solid.

Example 33

Substituted Benzyl Alcohol 36: To a solution of aldehyde 35 (0.80g, 1.35 mmol) in THF (9 mL) and H_2O (1 mL) at $-10°C$ was added $NaBH_4$ (0.13 g, 3.39 mmol). The reaction mixture was stirred for 1 h at $-10°C$ and the solvent was evaporated under reduced pressure. The

5   residue was dissolved in CH_2Cl_2 and washed with $NaHSO_4$, H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (6% 2-propanol/CH_2Cl_2) to give the alcohol (0.56 g, 70%) as a white solid.

Example 34

10   Substituted Benzyl Bromide 37: To a solution of alcohol 36 (77 mg, 0.13 mmol) in THF (1 mL) and CH_2Cl_2 (1 mL) at $0°C$ was added triethylamine (0.027 mL, 0.20 mmol) and methanesulfonyl chloride (0.011 mL, 0.14 mmol). The reaction mixture was stirred at $0°C$ for 30 min and warmed to room temperature for 3 h. Lithium bromide (60 mg, 0.69 mmol) was added and stirred for 45 min. The reaction mixture was concentrated and the residue was

15   partitioned between CH_2Cl_2 and H_2O, dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2% MeOH/CH_2Cl_2) to give the bromide (60 mg, 70%).

Example 35

20   Diethylphosphonate 38: A solution of bromide 37 (49 mg, 0.075 mmol) and triethylphosphite (0.13 mL, 0.75 mmol) in toluene (1.5 mL) was heated to $120°C$ and stirred overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (6% MeOH/CH_2Cl_2) to give the diethylphosphonate (35 mg, 66%, GS 191338) as a white

25   solid: ^1H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.27-7.16 (m, 4H), 7.00 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.1 Hz, 1H), 5.00 (m, 2H), 4.04-3.73 (m, 13H), 3.13-2.80 (m, 9H), 1.82-1.64 (m, 3H), 1.25 (t, J = 6.9 Hz, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR ($CDCl_3$) $\square$ 26.4; MS (ESI) 735 (M+Na).

30   Example 36

N-tert-Butoxycarbonyl-O-benzyl-L-serine 39: To a solution of Boc-L-serine (15 g, 73.09 mmol) in DMF (300 mL) at $0°C$ was added NaH (6.43 g, 160.80 mmol, 60% in mineral oil) and stirred for 1.5 h at $0°C$. After the addition of benzyl bromide (13.75 g, 80.40 mmol), the

reaction mixture was warmed to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in H_2O. The crude product was partitioned between H_2O and Et_2O. The aqueous phase was acidified to pH<4 with 3 N HCl and extracted with EtOAc three times. The combined EtOAc solution was washed with H_2O, dried with Na_2SO_4, filtered, and concentrated to give the N-tert-butoxycarbonyl-O-benzyl-L-serine (17.27 g, 80%).

Example 37

Diazo Ketone 40: To a solution of N-tert-Butoxycarbonyl-O-benzyl-L-serine 39 (10 g, 33.86 mmol) in dry THF (120 mL) at –15°C was added 4-methylmorpholine (3.8 mL, 34.54 mmol) followed by the slow addition of isobutylchloroformate (4.40 mL, 33.86 mmol). The reaction mixture was stirred for 30 min and diazomethane (~50 mmol, generated from 15 g Diazald according to Aldrichimica Acta 1983, 16, 3) in ether (~150 mL) was poured into the mixed anhydride solution. The reaction was stirred for 15 min and was then placed in an ice bath at 0°C and stirred for 1 h. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in EtOAc, washed with water, saturated $NaHCO_3$, saturated NaCl, dried with Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography (EtOAc/hexane) to afford the diazo ketone (7.50 g, 69%) as a yellow oil.

Example 38

Chloroketone 41: To a suspension of diazoketone 40 (7.50 g, 23.48 mmol) in ether (160 mL) at 0°C was added 4N HCl in dioxane (5.87 mL, 23.48 mmol). The reaction mixture was stirred at 0°C for 1 h. The reaction solvent was evaporated under reduced pressure to give the chloroketone which was used directly without any further purification.

Example 39

Chloroalcohol 42: To a solution of chloroketone 41 (7.70 g, 23.48 mmol) in THF (90 mL) was added water (10 mL) and the solution was cooled to 0°C. A solution of $NaBH_4$ (2.67 g, 70.45 mmol) in water (4 mL) was added dropwise over a period of 10 min. The mixture was stirred for 1 h at 0°C and saturated $KHSO_4$ was slowly added until the pH<4 followed by saturated NaCl. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column

chromatography on silica gel (1/4 EtOAc/hexane) to give the chloroalcohol (6.20 g, 80%) as a diastereomeric mixture.

Example 40

Epoxide 43: A solution of chloroalcohol 42 (6.20 g, 18.79 mmol) in EtOH (150 mL) was treated with 0.71 M KOH (1.27 g, 22.55 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated under reduced pressure and the residue was partitioned between EtOAc and water. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (1/6 EtOAc/hexane) to afford the desired epoxide 43 (2.79 g, 45%) and a mixture of diastereomers 44 (1.43 g, 23%).

Example 41

Sulfonamide 45: To a suspension of epoxide 43 (2.79 g, 8.46 mmol) in 2-propanol (30 mL) was added isobutylamine (8.40 mL, 84.60 mmol) and the solution was refluxed for 1 h. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH_2Cl_2 (40 mL) and cooled to 0°C. Triethylamine (2.36 mL, 16.92 mmol) was added followed by the addition of 4-methoxybenzenesulfonyl chloride (1.75 g, 8.46 mmol). The solution was stirred for 40 min at 0°C, warmed to room temperature, and evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was directly used without any further purification.

Example 42

Silyl Ether 46: A solution of sulfonamide 45 (5.10 g, 8.46 mmol) in CH_2Cl_2 (50 mL) was treated with triethylamine (4.7 mL, 33.82 mmol) and TMSOTf (3.88 mL, 16.91 mmol). The reaction mixture was stirred at room temperature for 1 h and partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic extracts were washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (1/6 EtOAc/hexane) to give the silyl ether (4.50 g, 84%) as a thick oil.

Example 43

Alcohol 47: To a solution of silyl ether 46 (4.5 g, 7.14 mmol) in MeOH (50 mL) was added

10% Pd/C (0.5 g). The suspension was stirred under H_2 atmosphere (balloon) at room

temperature for 2 h. The reaction mixture was filtered through a plug of celite and

5   concentrated under reduced pressure. The crude product was purified by column

chromatography on silica gel (3% MeOH/CH_2Cl_2) to give the alcohol (3.40 g, 85%) as a

white solid.

Example 44

10   Aldehyde 48: To a solution of alcohol 47 (0.60 g, 1.07 mmol) in CH_2Cl_2 (6 mL) at 0°C was

added Dess Martin reagent (0.77 g, 1.82 mmol). The reaction mixture was stirred at 0°C for

3 h and partitioned between CH_2Cl_2 and $NaHCO_3$. The organic phase was washed with H_2O,

dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column

chromatography on silica gel (1/4 EtOAc/hexane) to give the aldehyde (0.45 g, 75%) as a

15   pale yellow solid.

Example 45

Sulfonamide 50: To a suspension of epoxide (2.00 g, 5.41 mmol) in 2-propanol (20 mL) was

added amine 49 (4.03 g, 16.23 mmol) (prepared in 3 steps starting from 4-

20   (aminomethyl)piperidine according to Bioorg. Med. Chem. Lett., 2001, 11, 1261.). The

reaction mixture was heated to 80°C and stirred for 1 h. The solution was evaporated under

reduced pressure and the crude solid was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C.

Triethylamine (4.53 mL, 32.46 mmol) was added followed by the addition of 4-

methoxybenzenesulfonyl chloride (3.36 g, 16.23 mmol). The solution was stirred for 40 min

25   at 0°C, warmed to room temperature for 1.5 h, and evaporated under reduced pressure. The

residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic phase was

washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced

pressure. The crude product was purified by column chromatography on silica gel (3% 2-

propanol/CH_2Cl_2) to give the sulfonamide (2.50 g, 59%).

30

Example 46

Amine 51: A solution of sulfonamide 50 (2.50 g, 3.17 mmol) in CH_2Cl_2 (6 mL) at 0°C was

treated with trifluoroacetic acid (3 mL). The solution was stirred for 30 min at 0°C and then

warmed to room temperature for an additional 1.5 h. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2x), water (2x) and saturated NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure to give the amine (1.96 g, 90%)

5   which was used directly without any further purification.

Example 47

Carbamate 52: To a solution of amine 51 (1.96 g, 2.85 mmol) in CH$_3$CN (15mL) at 0°C was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (0.84g,

10   2.85mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and 4-(dimethylamino)pyridine (0.70 g, 5.70 mmol). After stirring for 2 h at 0°C, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5N NaOH (2 x), 5% citric acid (2 x), saturated NaHCO$_3$, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced

15   pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the carbamate (1.44 g, 60%) as a white solid.

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Example Section I

Example 1

Carbonate 2: To a solution of (R)-(+)-3-hydroxytetrahydrofuran (1.23 g, 14 mmol) in

5   CH$_2$Cl$_2$ (50 mL) was added triethylamine (2.9 mL, 21 mmol) and bis(4-nitrophenyl)carbonate (4.7 g, 15.4 mmol). The reaction mixture was stirred at room temperature for 24 h and partitioned between CH$_2$Cl$_2$ and saturated NaHCO$_3$. The CH$_2$Cl$_2$ layer was dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (2/1-EtOAc/hexane) to give the carbonate (2.3 g, 65%) as a pale

10   yellow oil which solidified upon standing.

Example 2

Carbamate 3: To a solution of 1 (0.385 g, 0.75 mmol) and 2 (0.210 g, 0.83 mmol) in CH$_3$CN (7 mL) at room temperature was added N, N-diisopropylethylamine (0.16 mL, 0.90 mmol).

15   The reaction mixture was stirred at room temperature for 44 h. The solvent was evaporated under reduced pressure. The crude product was dissolved in EtOAc and washed with saturated NaHCO$_3$, brine, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the carbamate (0.322 g, 69%) as a white solid: mp 98-100°C (uncorrected).

20

Example 3

Phenol 4: To a solution of 3 (0.31 g, 0.49 mmol) in EtOH (10 mL) and EtOAc (5 mL) was added 10% Pd/C (30 mg). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature for 15 h. The reaction mixture was filtered through a plug of celite. The

25   filtrate was concentrated and dried under vacuum to give the phenol (0.265 g) in quantitative yield.

Example 4

Diethylphosphonate 5: To a solution of phenol 4 (100 mg, 0.19 mmol) in THF (3 mL) was

30   added Cs$_2$CO$_3$ (124 mg, 0.38 mmol) and triflate (85 mg, 0.29 mmol). The reaction mixture was stirred at room temperature for 4 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH$_2$Cl$_2$) to

give the diethylphosphonate (63 mg, 49%, **GS 16573**) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.65 (d, J = 8.7Hz, 2H), 7.21 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 9 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.06 (broad, s, 1H), 4.80 (d, J = 7.5 Hz, 1H), 4.19 (m, 6H), 3.83 (s, 3H), 3.80-3.70 (m, 6H), 3.09-2.72 (m, 6H), 2.00 (m, 1H), 1.79 (m, 2H), 1.32 (t, J = 7.5 Hz, 6H), 0.86 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{31}P NMR δ 17.8.

Example 5

Dibenzylphosphonate 6: To a solution of phenol 4 (100 mg, 0.19 mmol) in THF (3 mL) was added Cs$_2$CO$_3$ (137 mg, 0.42 mmol) and triflate (165 mg, 0.39 mmol). The reaction mixture was stirred at room temperature for 6 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (5% 2-propanol/CH$_2$Cl$_2$) to give the dibenzylphosphonate (130 mg, 84%, **GS 16574**) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.65 (d, J = 9 Hz, 2H), 7.30 (m, 10H), 7.08 (d, J = 8.4Hz, 2H), 6.94 (d, J = 9 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 5.16-5.04 (m, 5H), 4.80 (d, J = 8.1 Hz, 1H), 4.16 (d, J = 10.2 Hz, 2H), 3.82 (s, 3H), 3.75-3.71 (m, 6H), 3.10-2.72 (m, 6H), 2.00 (m, 1H), 1.79 (m, 2H), 0.86 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 18.8.

Example 6

Phosphonic Acid 7: To a solution of 6 (66 mg, 0.08 mmol) in EtOH (3 mL) was added 10% Pd/C (12 mg). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature for 15 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated under reduced pressure and triturated with EtOAc to give the phosphonic acid (40 mg, 78%, **GS 16575**) as a white solid.

Example 7

Carbonate 8: To a solution of (S)-(+)-3-hydroxytetrahydrofuran (2 g, 22.7 mmol) in CH$_3$CN (50 mL) was added triethylamine (6.75 mL, 48.4 mmol) and N,N'-disuccinimidyl carbonate (6.4 g, 25 mmol). The reaction mixture was stirred at room temperature for 5 h and concentrated under reduced pressure. The residue was partitioned between EtOAc and H$_2$O. The organic phase was dried with Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc as eluant)

followed by recrystallization (EtOAc/hexane) to give the carbonate (2.3 g, 44%) as a white solid.

Example 8

5   Carbamate 9: To a solution of 1 (0.218 g, 0.42 mmol) and 8 (0.12 g, 0.53 mmol) in CH$_3$CN (3 mL) at room temperature was added N, N-diisopropylethylamine (0.11 mL, 0.63 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was partitioned between EtOAc and saturated NaHCO$_3$. The organic phase was washed with brine, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product

10   was purified by column chromatography on silica gel (1/1-EtOAc/hexane) to give the carbamate (0.176 g, 66%) as a white solid.

Example 9

Phenol 10: To a solution of 9 (0.176 g, 0.28 mmol) in EtOH (10 mL) was added 10% Pd/C

15   (20 mg). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature for 4 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phenol (0.151 g, **GS 10**) in quantitative yield.

Example 10

20   Diethylphosphonate 11: To a solution of phenol 10 (60 mg, 0.11 mmol) in THF (3 mL) was added Cs$_2$CO$_3$ (72 mg, 0.22 mmol) and triflate (66 mg, 0.22 mmol). The reaction mixture was stirred at room temperature for 4 h and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude

25   product was purified by column chromatography on silica gel (5% 2-propanol/CH$_2$Cl$_2$) to give the diethylphosphonate (38 mg, 49%, **GS 11**) as a white solid.

Example Section J

Example 1

Triflate 1: To a solution of A (4 g, 6.9 mmol) in THF (30 mL) and CH₂Cl₂ (10 mL) was

5   added Cs₂CO₃ (2.7 g, 8 mmol) and N-phenyltrifluoromethanesulfonimide (2.8 g, 8.0 mmol)

and stirred at room temperature for 16 h. The reaction mixture was concentrated under

reduced pressure. The residue wsa partitioned between CH₂Cl₂ and saturated brine twice.

The organic phase was dried over sodium sulfate and used for next reaction without further

purification.

10

Example 2

Aldehyde 2: A solution of crude above triflate 1 (~6.9 mmol) in DMF (20 mL) was degassed

(high vacumn for 5 min, argon purge, repeat 3 times). To this solution were quickly added

Pd(OAc)₂ (120 mg, 266 μmol) and bis(diphenylphosphino-propane (dppp ,220 mg, 266

15   μmol), and heated to 70°C. To this reaction mixture was rapidly introduced carbon

monoxide, and stirred at room temperature under an atmopheric pressure of carbon

monoxide, followed by slow addition of TEA (5.4 mL, 38 mmol) and triethylsilane (3 mL, 18

mmol). The resultant mixture was stirred at 70°C for 16 h, then cooled to room temperature,

concentrated under reduced pressure, partitioned between CH₂Cl₂ and saturated brine. The

20   organic phase was concentrated under reduced pressure and purified on silica gel column to

afford aldehyde 2 (2.1 g, 51%) as white solid.

Example 3

Compounds 3a-3e: Respresentative Procedure, 3c: A solution of aldehyde 2 (0.35 g, 0.59

25   mmol), L-alanine isopropyl ester hydrochloride (0.2 g, 1.18 mmol), glacial acetic acid (0.21

g, 3.5 mmol) in 1,2-dichloroethane (10 mL) was stirred at room temperature for 16 h,

followed by addition of sodium cyanoborohydride (0.22 g, 3.5 mmol) and methanol (0.5 mL).

The resulting solution was stirred at room temperature for one h. The reaction mixture was

washed with sodium bicarbonate solution, saturated brine, and chromatographed on silica gel

30   to afford 3c (0.17 g, 40%). ¹H NMR (CDCl₃): δ 7.72 (d, 2H), 7.26 (d, 2H), 7.20 (d, 2H), 7.0

(d, 2H), 5.65 (d, 1H), 4.90-5.30 (m, 3H), 3.53-4.0 (m overlapping s, 13H), 3.31 (q, 1H),

2.70-3.20 (m, 7H), 1.50-1.85 (m, 3H), 1.25-1.31 (m, 9H), 0.92 (d, 3H), 0.88 (d, 3H). MS: 706

(M + 1).

Compound	R₁	R₂	Amino Acid
3a	Me	Me	Ala
3b	Me	Et	Ala
3c	Me	iPr	Ala
3d	Me	Bn	Ala
3e	iPr	Et	Val

Example 4

Sulfonamide 1: To a solution of crude amine A (1 g, 3 mmol) in CH_2Cl_2 was added TEA

(0.6 g, 5.9 mmol) and 3-methoxybenzenesulfonyl chloride (0.6 g, 3 mmol). The resulting

solution was stirred at room temperature for 5 h, and evaporated under reduced pressure. The

residue was chromatographed on silica gel to afford sulfonamide 1 (1.0 g, 67%).

Example 5

Amine 2: To a 0°C cold solution of sulfonamide 1 (0.85 g, 1.6 mmol) in CH_2Cl_2 (40 mL)

was treated with BBr_3 in CH_2Cl_2 (10 mL of 1 M solution, 10 mmol). The solution was stirred

at 0°C 10 min and then warmed to room temperature and stirred for 1.5 h. The reaction

mixture was quenched with CH_3OH, concentrated under reduced pressure, azeotroped with

CH_3CN three times. The crude amine 2 was used for next reaction without further

purification.

Example 6

Carbamate 3: A solution of crude amine 2 (0.83 mmol) in CH_3CN (20 mL) and was treated

with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (245 mg, 0.83

mmol, prepared according to Ghosh et al., J. Med. Chem. 1996, 39, 3278.) and N,N-

dimethylaminopyridine (202 mg, 1.7 mmol). After stirring for 16 h at room temperature, the

reaction solvent was evaporated under reduced pressure and the residue was partitioned

between CH_2Cl_2 and saturated $NaHCO_3$ three times. The organic phase was evaporated

under reduced pressure. The residue was purified by chromatography on silica gel affording

the carbamate 3 (150 mg, 33%) as a solid.

Example 7

Diethylphosphonate 4: To a solution of carbamate 3(30 mg, 54 μmol) in THF (5 mL) was

added Cs$_2$CO$_3$ (54 mg, 164 μmol) and triflate # (33 mg, 109 μmol). After stirring the

reaction mixture for 30 min at room temperature, additional Cs$_2$CO$_3$ (20 mg, 61 μmol) and

triflate (15 mg, 50 μmol) were added and the mixture was stirred for 1 more hour. The

5   reaction mixture was evaporated under reduced pressure and the residue was partitioned

between CH$_2$Cl$_2$ and water. The organic phase was dried (Na$_2$SO$_4$), filtered and evaporated

under reduced pressure. The crude product was chromatographed on silica gel and repurified

by HPLC (50% CH$_3$CN-50% H$_2$O on C18 column) to give the diethylphosphonate 4 (15 mg,

39%). ^{1}H NMR (CDCl$_3$): δ 7.45 (m, 3H), 7.17-7.30 (m, 6H), 5.64 (d, 1H), 5.10 (d, 1H), 5.02

10   (q, 1H), 4.36 (d, 2H), 4.18-4.29 (2 q overlap, 4H), 3.60-3.98 (m, 7H), 2.70-3.10 (m, 7H),

1.80-1.90 (m, 1H), 1.44-1.70 (m, 2H + H2O), 1.38 (t, 6H), 0.94 (d, 3H), 0.90 (d, 3H). ^{31}P

NMR (CDCl$_3$): 18.7 ppm; MS (ESI) 699 (M + H).

Example 8

15   Dibenzylphosphonate 5: To a solution of carbamate 3 (100 mg, 182 μmol) in THF (10 mL)

was added Cs$_2$CO$_3$ (180 mg, 550 μmol) and dibenzylhydroxymethyl phosphonate triflate,

Section A, Scheme 2, Compound 9, (150 mg, 360 μmol). After stirring the reaction mixture

for 1 h at room temperature, the reaction mixture was evaporated under reduced pressure and

the residue was partitioned between CH$_2$Cl$_2$ and water. The organic phase was dried

20   (Na$_2$SO$_4$), filtered and evaporated under reduced pressure. The residue was purified by

HPLC (50% CH$_3$CN-50% H$_2$O on C18 column) to give the dibenzylphosphonate 5 (110 mg,

72%). ^{1}H NMR (CDCl$_3$): δ 7.41 (d, 2H), 7.35 (s, 10 H), 7.17-7.30 (m, 6H), 7.09-7.11 (m,

1H), 5.64 (d, 1H), 4.90-5.15 (m, 6H), 4.26 (d, 2H), 3.81-3.95 (m, 4H), 3.64-3.70 (m, 2H),

2.85-3.25 (m, 7H), 1.80-1.95 (m, 1H), 1.35-1.50 (m, 1H), 0.94 (d, 3H), 0.91 (d, 3H). ^{31}P

25   NMR (CDCl$_3$) δ 19.4 ppm; MS (ESI): 845 (M + Na), 1666 (2M + Na).

Example 9

Phosphonic acid 6: A solution of dibenzylphosphonate 5 (85 mg, 0.1 mmol) was dissolved in

MeOH (10 mL) treated with 10% Pd/C (40 mg) and stirred under H$_2$ atmosphere (balloon)

30   overnight. The reaction was purged with N$_2$, and the catalyst was removed by filtration

through celite. The filtrate was evaporated under reduced pressure to afford phosphonic acid

6 (67 mg, quantitatively). ^{1}H NMR (CD$_3$OD): δ 7.40-7.55 (m, 3H), 7.10-7.35 (m, 6H), 5.57

(d, 1H), 4.32 (d, 2H), 3.90-3.95 (m, 1H), 3.64-3.78 (m, 5H), 3.47 (m, 1H), 2.85-3.31 (m,

5H), 2.50-2.60 (m, 1H), 2.00-2.06 (m, 1H), 1.46-1.60 (m, 1H), 1.30-1.34 (m, 1H), 0.9 (d,

3H), 0.90 (d, 3H). ^{31}P NMR (CD$_3$OD): 16.60 ppm; MS (ESI): 641 (M – H).

5   Example 10

Sulfonamide 1: To a solution of crude amine A (0.67 g, 2 mmol) in CH$_2$Cl$_2$ (50 mL) was

added TEA (0.24 g, 24 mmol) and crude 3-acetoxy-4-methoxybenzenesulfonyl chloride (0.58

g, 2.1 mmol, was prepared according to Kratzl et al., Monatsh. Chem.1952, 83, 1042-1043),

and the solution was stirred at room temperature for 4 h, and evaporated under reduced

10   pressure. The residue was chromatographed on silica gel to afford sulfonamide 1 (0.64 g,

54%). MS: 587 (M + Na), 1150 (2M + Na)

Phenol 2: Sulfonamide 1 (0.64 g, 1.1 mmol) was treated with saturated NH$_3$ in MeOH (15

mL) at room temperature for 15 min., then evaporated under reduced pressure. The residue

15   was purified on silica gel column to afford phenol 2 (0.57 g, 96%).

Example 11

Dibenzylphosphonate 3a: To a solution of phenol 2 (0.3 g, 0.57 mmol) in THF (8 mL) was

added Cs$_2$CO$_3$ (0.55 g, 1.7 mmol)) and dibenzylhydroxymethyl phosphonate triflate (0.5 g,

20   1.1 mmol). After stirring the reaction mixture for 1 h at room temperature, the reaction

mixture was quenched with water and partitioned between CH$_2$Cl$_2$ and saturated ammonium

chloride aqueous solution. The organic phase was dried (Na$_2$SO$_4$), filtered and evaporated

under reduced pressure. The residue was chromatographed on silica gel (40% EtOAc/ 60%

hexane) to give the dibenzylphosphonate 3a (0.36 g, 82%). ^{1}H NMR (CDCl$_3$): δ 7.20-7.40

25   (m, 17H), 6.91 (d, 1H), 5.10-5.25 (2 q(ab) overlap, 4H), 4.58-4.70 (m, 1H), 4.34 (d, 2H),

3.66-3.87 (m + s, 5H), 2.85-3.25 (m, 6H), 1.80-1.95 (m, 1H), 1.58 (s, 9H), 0.86-0.92 (2d,

6H).

Example 12

30   Diethylphosphonate 3b: To a solution of phenol 2 (0.15 g, 0.28 mmol) in THF (4 mL) was

added Cs$_2$CO$_3$ (0.3 g, 0.92 mmol)) and diethylhydroxymethyl phosphonate triflate (0.4 g, 1.3

mmol). After stirring the reaction mixture for 1 h at room temperature, the reaction mixture

was quenched with water and partitioned between CH$_2$Cl$_2$ and saturated NaHCO$_3$ aqueous

solution. The organic phase was dried (Na₂SO₄), filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel (1% CH₃OH-CH₂Cl₂) to give the diethylphosphonate 3b (0.14 g, 73%).

<p>5</p>

Example 13

Amine 4a: To a solution of 3a (0.35 g, 0.44 mmol) in CH₂Cl₂ (10 mL) was treated with TFA (0.75 g, 6.6 mmol) at room temperature for 2 h. The reaction was evaporated under reduced pressure, azeotroped with CH₃CN twice, dried to afford crude amine 4a. This crude 4a was used for next reaction without further purification.

<p>10</p>

Example 14

Amine 4b: To a solution of 3b (60 mg, 89 μmol) in CH₂Cl₂ (1 mL) was treated with TFA (0.1 mL, 1.2 mmol) at room temperature for 2 h. The reaction was evaporated under reduced pressure, azeotroped with CH₃CN twice, dried to afford crude amine 4b (68 mg). This crude
<p>15</p> 4b was used for next reaction without further purification.

Example 15

Carbamate 5a: An ice-cold solution of crude amine 4a (0.44 mmol) in CH₃CN (10 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate
<p>20</p> (120 mg, 0.4 mmol) and N,N-dimethylaminopyridine (DMAP, 110 mg, 0.88 mmol). After 4 h, more DMAP (0.55 g, 4.4 mmol) was added to the reaction mixture. After stirring for 1.5 h at room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH₂Cl₂ and saturated NaHCO₃. The organic phase was evaporated under reduced pressure. The residue was purified by chromatography on silica
<p>25</p> gel affording the crude carbamate 5a (220 mg) containing some p-nitrophenol. The crude 5a was repurified by HPLC (50% CH₃CN /50% H₂O) to afford pure carbamate 5a (176 mg, 46%, 2 steps). ¹H NMR (CDCl₃): δ 7.20-7.36 (m, 1H), 6.94 (d, 1H), 5.64 (d, 1H), 5.10-5.25 (2 q(ab) overlap, 4H), 4.90-5.10 (m, 1H), 4.90 (d, 1H), 4.34 (d, 2H), 3.82-3.91 (m + s, 6H), 3.63-3.70 (m, 3H), 2.79-3.30 (m, 7H), 1.80-1.90 (m, 1H), 1.40-1.50 (m, 1H), 0.94 (d, 3H),
<p>30</p> 0.89 (d, 3H). ³¹P NMR (CDCl₃): 17.2 ppm.

Example 16

<p>457</p>

Carbamate 5b: An ice-cold solution of crude amine 4b (89 µmol)) in CH_3CN (5 mL) and was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-*b*]furan-2-yl 4-nitrophenyl carbonate (26mg, 89 µmol) and N,N-dimethylaminopyridine (DMAP, 22 mg, 0.17 mmol). After 1 h at 0°C, more DMAP (10 mg. 82 µmol) was added to the reaction mixture. After stirring for 2 h at

5   room temperature, the reaction solvent was evaporated under reduced pressure and the residue was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was evaporated under reduced pressure. The residue was purified by HPLC (C18 column, 45% $CH_3CN/55\%$ H_2O) to afford pure carbamate 5b (18.8 mg, 29%, 3 steps). ^1H NMR $(CDCl_3)$: δ 7.38 (d, 2H), 7.20-7.36 (m, 6H), 7.0 (d, 1H), 5.64 (d, 1H), 4.96-5.03 (m, 2H), 4.39 (d, 2H),

10   4.20-4.31 (2q overlap, 4H) 3.80-4.00 ((s overlap with m, 7H), 3.60-3.73 (m, 2H), 3.64-3.70 (m, 2H), 2.85-3.30 (m, 7H), 1.80-1.95 (m, 1H), 1.55-1.75 (m, 1H), 1.35-1.50 (s overlap with m, 7H), 0.94 (d, 3H), 0.88 (d, 3H). ^{31}P NMR $(CDCl_3)$: 18.1ppm.

Example 17

15   Phosphonic acid 6: A solution of dibenzylphosphonate 5a (50 mg, 58 µmol) was dissolved in MeOH (5 mL) and EtOAc (3 mL) and treated with 10% Pd/C (25 mg) and was stirred at room temperature under H_2 atmosphere (balloon) for 8 h. The catalyst was filtered off. The filtrate was concentrated and redissolved in MeOH (5 mL), treated with 10% Pd/C (25 mg) and was stirred at room temperature under H_2 atmosphere (balloon) overnight. The catalyst

20   was filtered off. The filtrate was evaporated under reduced pressure to afford phosphonic acid 6 (38 mg, quantitatively). ^1H NMR (CD_3OD): δ 7.42 (m, 1H), 7.36 (s, 1H), 7.10-7.25 (m, 6H), 5.58 7 (d, 1H), 4.32 (d, 2H), 3.90 (s, 3H), 3.60-3.80 (m, 6H), 3.38 (d, 1H), 2.85-3.25 (m, 5H), 2.50-2.60 (m, 1H), 1.95-2.06 (m, 1H), 1.46-1.60 (m, 1H), 1.30-1.40 (m, 1H), 0.93(d, 3H), 0.89 (d, 3H). ^{31}P NMR (CD_3OD): 14.8 ppm; MS (ESI): 671 (M – H).

25

Example 18

Amine 7: To a 0°C cold solution of diethylphosphonate 3b (80 mg, 0.118 mmol) in CH_2Cl_2 was treated with BBr_3 in CH_2Cl_2 (0.1 mL of 1 M solution, 1 mmol). The solution was stirred at 0°C 10 min and then warmed to room temperature and stirred for 3 h. The reaction

30   mixture was concentrated under reduced pressure. The residue was redissolved in CH_2Cl_2 (containing some CH_3OH, concentrated, azeotroped with CH_3CN three times. The crude amine 7 was used for next reaction without further purification.

Example 19

Carbamate 8: An ice-cold solution of crude amine 7 (0.118 mmol) in CH$_3$CN (5 mL) and
was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (35
mg, 0.118 mmol) and N,N-dimethylaminopyridine (29 mg, 0.24mmol), warmed to room
temperature. After stirring for 1 h at room temperature, more DMAP (20 mg, 0.16 mmol)
was added to reaction mixture. After 2 h stirred at room temperature, the reaction solvent
was evaporated under reduced pressure and the residue was partitioned between CH$_2$Cl$_2$ and
saturated NaHCO$_3$. The organic phase was evaporated under reduced pressure. The residue
was purified by HPLC on C18 (CH$_3$CN-55%H$_2$O) to afford the desired carbamate 8 (11.4
mg, 13.4%) as an off-white solid. ^{1}H NMR (CDCl$_3$): δ 7.20-7.40 (m, 7H), 7.00 (d, 1H), 5.64
(d, 1H), 5.00-5.31 (m, 2H), 4.35 (d, 2H), 4.19-4.30 (2q overlap, 4H), 3.80-4.00 (m, 4H), 3.68-
3.74 (m, 2H), 3.08-3.20 (m, 3H), 2.75-3.00 (m, 4H), 1.80-1.90 (m, 1H), 1.55-1.75 (m, 1H),
1.38 (t, 6H), 0.91 (2d overlap, 6H). ^{31}P NMR (CD$_3$OD): δ19.5 ppm.

Example Section K

Example 1

Monophenyl-monolactate 3: A mixture of monoacid 1 (0.500 g, 0.7 mmol), alcohol 2 (0.276

5   g, 2.09 mmol) and dicyclohexylcarbodiimide (0.431 g, 2.09 mmol) in dry pyridine (4 mL) was placed into a 70°C oil bath and heated for two hours. The reaction was monitored by TLC assay (SiO$_2$, 70% ethyl acetate in hexanes as eluent, product R$_f$ = 0.68, visualization by UV). The reaction contents were cooled to ambient temperature with the aid of a cool bath and diluted with dichloromethane (25 mL). TLC assay may show presence of starting

10   material. The diluted reaction mixture was filtered to remove solids. The filtrate was then cooled to 0°C and charged with 0.1 N HCl (10 mL). The pH 4 mixture was stirred for 10 minutes and poured into separatory funnel to allow the layers to separate. The lower organic layer was collected and dried over sodium sulfate. The drying agent was filtered off and the filtrate concentrated to an oil via rotary evaporator (< 30°C warm bath). The crude product

15   oil was purified on pretreated silica gel (deactivated using 10% methanol in dichlorormethane followed by rinse with 60% ethyl acetate in dichloromethane). The product was eluted with 60% ethyl acetate in dichloromethane to afford the product monophenyl-monolactate 3 as a white foam (0.497 g, 86% yield). ^{1}H NMR (CDCl$_3$) δ 7.75 (d, 2H), 7.40-7.00 (m, 14H), 5.65 (d, 1H), 5.20-4.90 (m, 4H), 4.70 (d, 1H), 4.55-4.50 (m, 1H), 4.00-3.80 (m, 4H), 3.80-3.60 (m,

20   3H), 3.25-2.75 (m, 7H), 1.50 (d, 3H), 1.30-1.20 (m, 7H), 0.95 (d, 3H), 0.85 (d, 3H). ^{31}P NMR (CDCl$_3$) δ 16.2, 13.9.

Example 2

Monophenyl-monoamidate 5: A mixture of monoacid 1 (0.500 g, 0.70 mmol), amine

25   hydrochloride 4 (0.467 g, 2.78 mmol) and dicyclohexylcarbodiimide (0.862 g, 4.18 mmol) in dry pyridine (8 mL) was placed into a 60°C oil bath, and heated for one hour (at this temperature, product degrades if heating continues beyond this point). The reaction was monitored by TLC assay (SiO$_2$, 70% ethyl acetate in hexanes as eluent, product R$_f$ = 0.39, visualization by UV). The contents were cooled to ambient temperature and diluted with

30   ethyl acetate (15 mL) to precipitate a white solid. The mixture was filtered to remove solids and the filtrate was concentrated via rotary evaporator to an oil. The oil was diluted with dichloromethane (20 mL) and washed with 0.1 N HCl (2 x 20 mL), water (1 x 20 mL) and dilute sodium bicarbonate (1 x 20 mL). The organic layer was dried over sodium sulfate,

filtered, and concentrated to an oil via rotary evaporator. The crude product oil was dissolved in dichloromethane (10 mL). Hexane was slowly charged to the stirring solution until cloudiness persisted. The cloudy mixture was stirred for a few mintues until TLC assay showed that the dichloromethane/hexane layer contained no product. The

5   dichloromethane/hexanes layer was decanted and the solid was further purified on silica gel first pretreated with 10% methanol in ethyl acetate and rinsed with 50% ethyl acetate in hexanes. The product 5 was eluted with 50% ethyl acetate in hexanes to afford a white foam (0.255 g, 44% yield) upon removal of solvents. ^{1}H NMR (CDCl$_3$) δ 7.75 (d, 2H), 7.40-7.15 (m, 10H), 7.15-7.00 (t, 2H), 5.65 (d, 1H), 5.10-4.90 (m, 3H), 4.50-4.35 (m, 2H), 4.25-4.10

10   (m, 1H), 4.00-3.60 (m, 8H), 3.20-2.75 (m, 7H), 1.40-1.20 (m, 11H), 0.95 (d, 3H), 0.85 (d, 3H). ^{31}P NMR (CDCl$_3$) δ 19.1, 18.0.

Example 3

Bisamidate 8: A solution of triphenylphosphine (1.71 g, 6.54 mmol) and aldrithiol (1.44 g,

15   6.54 mmol) in dry pyridine (5 mL), stirred for at least 20 minutes at room temperature, was charged into a solution of diacid 6 (1.20 g, 1.87 mmol) and amine hydrochloride 7 (1.30 g, 7.47 mmol) in dry pyridine (10 mL). Diisopropylethylamine (0.97 g, 7.48 mmol) was then added to this combined solution and the contents were stirred at room temperature for 20 hours. The reaction was monitored by TLC assay (SiO$_2$, 5:5:1 ethyl

20   acetate/hexanes/methanol as eluent, product R$_f$ = 0.29, visualization by UV). The reaction mixture was concentrated via rotary evaporator and dissolved in dichloromethane (50 mL). Brine (25 mL) was charged to wash the organic layer. The aqueous layer was back extracted with dichloromethane (1 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated via rotary evaporator to afford an oil. The crude product oil

25   was purified on silica gel using 4% isopropanol in dichloromethane as eluent. The combined fractions containing the product may have residual amine contamination. If so, the fractions were concentrated via rotary evaporator and further purified by silica gel chromatography using a gradient of 1:1 ethyl acetate/hexanes to 5:5:1 ethyl acetate/hexanes/methanol solution as eluent to afford the product 8 as a foam (0.500 g, 30% yield).

30

Example 4

Diacid 6: A solution of dibenzylphosphonate 9 (8.0 g, 9.72 mmol) in ethanol (160 mL) and ethyl acetate (65 mL) under a nitrogen atmosphere and at room temperature was charged 10%

Pd/C (1.60 g, 20 wt%). The mixture was stirred and evacuated by vacuum and purged with hydrogen several times. The contents were then placed under atmospheric pressure of hydrogen via a balloon. The reaction was monitored by TLC assay (SiO$_2$, 7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, product R$_f$ = 0.05, visualization by UV) and was judged complete in 4 to 5 hours. The reaction mixture was filtered through a pad of celite to remove Pd/C and the filter cake rinsed with ethanol/ethyl acetate mixture (50 mL). The filtrate was concentrated via rotary evaporation followed by several co-evaporations using ethyl acetate (3 x 50 mL) to remove ethanol. The semi-solid diacid 6, free of ethanol, was carried forward to the next step without purification.

Example 5

Diphenylphosphonate 10: To a solution of diacid 6 (5.6 g, 8.71 mmol) in pyridine (58 mL) at room temperature was charged phenol (5.95 g, 63.1 mmol). To this mixture, while stirring, was charged dicyclohexylcarbodiimide (7.45 g, 36.0 mmol). The resulting cloudy, yellow mixture was placed in a 70-80°C oil bath. The reaction was monitored by TLC assay (SiO$_2$, 7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, diacid R$_f$ = 0.05, visualization by UV for the disappearance of starting material. SiO$_2$, 60% ethyl acetate in hexanes as eluent, diphenyl R$_f$ = 0.40, visualization by UV) and was judged complete in 2 hours. To the reaction mixture was charged isopropyl acetate (60 mL) to produce a white precipitation. The slurry was filtered through a pad of celite to remove the white precipitate and the filter cake rinsed with isopropyl acetate (25 mL). The filtrate was concentrated via rotary evaporator. To the resulting yellow oil was charged a premixed solution of water (58 mL) and 1N HCl (55 mL) followed by isopropyl acetate (145 mL). The mixture was stirred for one hour in an ice bath. After separating the layers, the aqueous layer was back extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated via rotary evaporator. The crude product oil was purified by silica gel column chromatography using 50% ethyl acetate in hexanes as eluent to afford the product 10 as a white foam (3.52 g, 51% yield). ^{1}H NMR (CDCl$_3$) δ 7.75 (d, 2H), 7.40-7.20 (m, 15H), 7.10 (d, 2H), 5.65 (d, 1H), 5.10-4.90 (m, 2H), 4.65 (d, 2H), 4.00-3.80 (m, 4H), 3.75-3.65 (m, 3H), 3.25-2.75 (m, 7H), 1.90-1.75 (m, 1H), 1.70-1.60 (m, 1H), 1.50-1.40 (m, 1H), 0.90 (d, 3H), 0.85 (d, 3H). ^{31}P NMR (CDCl$_3$) δ 10.9.

Example 6

Monophenyl 1: To a solution of diphenyl 10 (3.40 g, 4.28 mmol) in acetonitrile (170 mL) at

0°C was charged 1N sodium hydroxide (4.28 mL). The reaction was monitored by TLC

assay (SiO$_2$, 7:2.5:0.5 dichloromethane/methanol/ammonium hydroxide as eluent, diphenyl

R_f = 0.65, visualization by UV for the disappearance of starting material. Product

5   monophenyl R_f = 0.80, visualization by UV). Additional 1N NaOH was added (if necessary)

until the reaction was judged complete. To the reaction contents at 0°C was charged Dowex

H$^+$ (Dowex 50WX8-200) (4.42 g) and stirred for 30 minutes at which time the pH of the

mixture reached pH 1 (monitored by pH paper). The mixture was filtered to remove the

Dowex resin and the filtrate was concentrated via rotary evaporation (water bath < 40°C).

10   The resulting solution was co-evaporated with toluene to remove water (3 x 50 mL). The

white foam was dissolved in ethyl acetate (8 mL) followed by slow addition of hexanes (16

mL) over 30 minutes to induce precipitation. A premixed solution of 2:1 hexnaes/ethyl

acetate solution (39 mL) was charged to the precipitated material and stirred. The product 1

was filtered and rinsed with premixed solution of 2:1 hexanes/ethyl acetate solution (75 mL)

15   and dried under vacuum to afford a white powder (2.84 g, 92% yield). ^{1}H NMR (CD$_3$OD) δ

7.80 (d, 2H), 7.40-7.30 (m, 2H), 7.20-7.15 (m, 11H), 5.55 (d, 1H), 4.50 (d, 2H), 3.95-3.85 (m,

1H), 3.80-3.60 (m, 5H), 3.45 (bd, 1H), 3.25-3.15 (m, 2H), 3.00-2.80 (m, 3H), 2.60-2.45 (m,

1H), 2.10-1.95 (m, 2H), 1.85-1.60 (m, 2H), 1.50-1.40 (m, 1H), 1.40-1.30 (m, 1H), 0.95 (d,

3H), 0.85 (d, 3H). ^{31}P NMR (CDCl$_3$) δ 13.8. The monophenyl product 1 is sensitive to silica

20   gel. On contact with silica gel 1 converts to an unknown compound possessing ^{31}P NMR

chemical shift of 8 ppm. However, the desired monophenyl product 1 can be regenerated by

treatment of the unknown compound with 2.5 M NaOH in acetonitrile at 0°C for one hour

followed by Dowex H$^+$ treatment as described above.

25   Example 7

Dibenzylphosphonate 9: To a solution of phenol 11 (6.45 g, 11.8 mmol) in tetrahydrofuran

(161 mL) at room temperature was charged triflate reagent 12 (6.48 g, 15.3 mmol). Cesium

carbonate (11.5 g, 35.3 mmol) was added and the mixture was stirred and monitored by TLC

assay (SiO$_2$, 5% methanol in dichloromethane as eluent, dibenzyl product R_f = 0.26,

30   visualization by UV or ninhydrin stain and heat). Additional Cs$_2$CO$_3$ was added until the

reaction was judged complete. To the reaction contents was charged water (160 mL) and the

mixture extracted with ethyl acetate (2 x 160 mL). The combined organic layer was dried

over sodium sulfate, filtered, and concentrated via rotary evaporator to afford a viscous oil.

The crude oil was purified by silica gel column chromatography using a gradient of 100% dichloromethane to 1% methanol in dichloromethane to afford product 9 as a white foam (8.68 g, 90% yield). ^{1}H NMR (CDCl$_3$) δ 7.75 (d, 2H), 7.40-7.20 (m, 16H), 6.95 (d, 2H), 5.65 (d, 1H), 5.20-4.90 (m, 6H), 4.25 (d, 2H), 4.00-3.80 (m, 4H), 3.75-3.65 (m, 3H), 3.20-2.75 (m, 7H), 1.90-1.75 (m, 1H), 1.30-1.20 (m, 1H), 0.90 (d, 3H), 0.85 (d, 3H). ^{31}P NMR (CDCl$_3$) δ 19.1.

Example 7a

Hydroxyphenylsulfonamide 14: To a solution of methoxyphenylsulfonamide 13 (35.9 g, 70.8 mmol) in dichloromethane (3.5 L) at 0°C was charged boron tribromide (1M in DCM, 40.1 mL, 425 mmol). The reaction content was allowed to warm to room temperature, stirred over two hours, and monitored by TLC assay (SiO$_2$, 10% methanol in dichloromethane as eluent, dibenzyl product R$_f$ = 0.16, visualization by UV). To the contents at 0°C was slowly charged propylene oxide (82 g, 1.42 mmol). Methanol (200 mL) was added and the reaction mixture was concentrated via rotary evaporator to afford a viscous oil. The crude product mixture was purified by silica gel column chromatography using 10% methanol in dichloromethane to afford the product 14 as a foam (22 g, 80% yield). ^{1}H NMR (DMSO) δ 7.60 (d, 2H), 7.30-7.20 (m, 5H), 6.95 (d, 2H), 3.90-3.75 (m, 1H), 3.45-3.20 (m, 5H), 3.00-2.55 (m, 5H), 2.50-2.40 (m, 1H), 1.95-1.85 (m, 1H), 0.85 (d, 3H), 0.80 (d, 3H).

Example 8

Cisfuran carbamate 16: To a solution of amine 14 (20.4 g, 52.0 mmol) in acetonitrile (600 mL) at room temperature was charged dimethylaminopyridine (13.4 g, 109 mmol) followed by cisfuran p-nitrophenylcarbonate reagent 15 (14.6 g, 49.5 mmol). The resulting solution was stirred at room temperature for at least 48 hours and monitored by TLC assay (SiO$_2$, 10% methanol in dichloromethane as eluent, cisfuran product R$_f$ = 0.34, visualization by UV). The reaction mixture was concentrated via rotary evaporator. The crude product mixture was purified by silica gel column chromatography using a gradient of 60% ethyl acetate in hexanes to 70% ethyl acetate in hexanes to afford the product 16 as a solid (18.2 g, 64% yield). ^{1}H NMR (DMSO) δ 10.4 (bs, 1H), 7.60 (d, 2H), 7.30-7.10 (m, 6H), 6.95 (d, 2H), 5.50 (d, 1H), 4.85 (m, 1H), 3.85 (m, 1H), 3.70 (m, 1H), 3.65-3.50 (m, 4H), 3.30 (d, 1H), 3.05-2.95 (m, 2H), 2.80-2.65 (m, 3H), 2.50-2.40 (m, 1H), 2.00-1.90 (m, 1H), 1.45-1.20 (m, 2H), 0.85 (d, 3H), 0.80 (d, 3H).

Example Section L

Example 1

Monobenzyl phosphonate 2 A solution of dibenzylphosphonate 1(150 mg, 0.175mmol) was
dissolved in toluene (1 mL), treated with DABCO (20 mg, 0.178 mmol) and was refluxed
under N2 atmosphere (balloon) for 3 h. The solvent was removed and the residual was
dissolved in aqueous HCl (5%). The aqueous layer was extracted with ethyl acetate and the
organic layer was dried over sodium sulfate. After evaporation to yield the monobenzyl
phosphonate 2 (107 mg, 80%) as a white powder. ^{1}H NMR (CD$_3$OD) δ 7.75 (d, J = 5.4 Hz,
2H), 7.42-7.31 (m, 5H) 7.16 (d, J = 5.4 Hz, 2H), 7.01 (d, J = 5.4 Hz, 2H), 6.86 (d, J = 5.4 Hz,
2H), 5.55 (d, J = 3.3 Hz, 1H), 5.14 (d, J = 5.1 Hz, 2H), 4.91 (m, 1H), 4.24-3.66 (m
overlapping s, 11H), 3.45 (m, 2H), 3.14-2.82 (m, 6H), 2.49 (m, 1H), 2.01 (m, 1H), 1.51-1.34
(m, 2H), 0.92 (d, J = 3.9 Hz, 3H), 0.87 (d, J = 3.9 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 20.5; MS
(ESI) 761 (M-H).

Example 2

Monobenzyl, ethyl phosphonate 3 To a solution of monobenzyl phosphonate 2 (100 mg, 0.13
mmol) in dry THF (5 mL) at room temperature under N$_2$ was added Ph$_3$P (136 mg, 0.52
mmol) and ethanol (30 µL, 0.52 mmol). After cooled to 0°C, DEAD (78µL, 0.52 mmol) was
added. The mixture was stirred for 20 h at room temperature. The solvent was evaporated
under reduced pressure and the residue was purified by using chromatograph on silica gel
(10% to 30% ethyl acetate / hexane) to afford the monobenzyl, ethyl phosphonate 3 (66 mg,
64%) as white solid. ^{1}H NMR (CDCl$_3$) 7.70 (d, J = 8.7 Hz, 2H), 7.43-7.34 (m, 5H) 7.14 (d,
J = 8.4 Hz, 2H), 7.01 (d, J = 8.7Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.56 (d, J = 5.4 Hz, 1H),
5.19 (d, J = 8.7 Hz, 2H), 5.00 (m, 2H), 4.22-3.67 (m overlapping s, 13H), 3.18-2.76 (m, 7H),
1.82-1.54 (m, 3H), 1.33 (t, J = 7.0 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H);
^{31}P NMR (CDCl$_3$) δ 19.8; MS (ESI) 813 (M+Na).

Example 3

Monoethyl phosphonate 4 A solution of monobenzyl, ethyl phosphonate 3 (60 mg) was
dissolved in EtOAc (2 mL), treated with 10% Pd/C (6 mg) and was stirred under H$_2$
atmosphere (balloon) for 2h. The catalyst was removed by filtration through celite. The
filtered was evaporated under reduced pressure, the residue was triturated with ether and the

solid was collected by filtration to afford the monoethyl phosphonate 4 (50 mg, 94%) as white solid. ^{1}H NMR (CD$_3$OD) 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.7Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 5.58 (d, J = 5.4 Hz, 1H), 5.90 (m, 1H), 4.22-3.67 (m overlapping s, 13H), 3.18-2.50 (m, 7H), 1.98(m, 1H), 1.56 (m, 2H), 1.33 (t, J = 6.9 Hz, 3H),

5   0.92 (d, J = 6.6Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 18.7; MS (ESI) 700 (M-H).

Example 4

Monophenyl, ethyl phosphonate 5 To a solution of phosphonic acid 11 (800 mg, 1.19 mmol)

10   and phenol (1.12 g, 11.9 mmol) in pyridine (8 mL) was added ethanol (69 μL, 1.19 mmol) and 1, 3-dicyclohexylcarbodiimide (1g, 4.8 mmol). The solution was stirred at 70°C for 2h. The reaction mixture was cooled to room temperature, then diluted with ethyl acetate (10 mL) and filtered. The filtrate was evaporated under reduced pressure to remove pyridine. The residue was dissolved in ethyl acetate and the organic phase was separated and washed

15   with brine, dried over MgSO4, filtered and concentrated. The residue was purified by chromatography on silica gel to give monophenyl, ethyl phosphonate 5 (600 mg, 65%) as white solid. ^{1}H NMR (CDCl$_3$) 7.72 (d, J = 9 Hz, 2H), 7.36-7.18 (m, 5H), 7.15 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 9Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.64 (d, J = 5.4 Hz, 1H), 5.00 (m, 2H), 4.34 (m, 4H), 3.94-3.67 (m overlapping s, 9H), 3.18-2.77 (m, 7H), 1.82-1.54 (m, 3H),

20   1.36 (t, J = 7.2 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 16.1; MS (ESI) 799 (M+Na).

Example 5

Sulfonamide 6 To a suspension of epoxide 5 (3 g, 8.12 mmol) in 2-propanol (30 mL) was

25   added isobutylamine (8 mL, 81.2 mmol) and the solution was stirred at 80°C for 1 h. The solution was evaporated under reduced pressure and the crude solid was dissolved in CH$_2$Cl$_2$ (40 mL) and cooled to 0°C. TEA (2.3 mL, 16.3mmol) was added followed by the addition of 4-nitrobenzenesulfonyl chloride (1.8 g, 8.13 mmol) in CH$_2$Cl$_2$ (5 mL) and the solution was stirred for 30 min at 0°C, warmed to room temperature and evaporated under reduced

30   pressure. The residue was partitioned between EtOAc and saturated NaHCO$_3$. The organic phase was washed with saturated NaCl, dried over Na$_2$SO$_4$, filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc/hexane to give the sulfonamide 6 (4.6 g, 91%) as an off-white solid. MS (ESI) 650 (M+Na).

Example 6

Phenol 7 A solution of sulfonamide 6 (4.5 g, 7.1 mmol) in CH$_2$Cl$_2$ (50 mL) at 0°C was

treated with BBr$_3$ (1M in CH$_2$Cl$_2$, 50mL). The solution was stirred at 0°C to room

5   temperature for 48h. CH$_3$OH (10 mL) was carefully added. The solvent was evaporated

under reduced pressure and the residue was partitioned between EtOAc and saturated

NaHCO$_3$. The organic phase washed with saturated NaCl, dried over Na$_2$SO$_4$, filtered, and

evaporated under reduced pressure. The crude product was purified by chromatography on

silica gel (10% - MeOH/CH$_2$Cl$_2$) to give the phenol 7 (2.5 g, 80%) as an off-white solid. MS

10   (ESI) 528 (M+H).

Example 7

Carbamate 8 A solution of sulfonamide 7 (2.5 g, 5.7 mmol) in CH$_3$CN (100 mL) and was

treated with proton-sponge (3 g, 14 mmol) and followed by (3R, 3aR, 6aS)-hexahydrofuro[2,

15   3-b]furan-2-yl 4-nitrophenyl carbonate (1.7 g, 5.7 mmol) at 0°C. After stirring for 48h at

room temperature, the reaction solvent was evaporated under reduced pressure and the

residue was partitioned between EtOAc and 10% HCl. The organic phase was washed with

saturated NaCl, dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The

crude product was purified by chromatography on silica gel (10% MeOH/CH$_2$Cl$_2$) affording

20   the carbamate 8 (2.1g, 62 %) as a white solid. MS (ESI) 616 (M+Na).

Example 8

Diethylphosphonate 9 To a solution of carbamate 8 (2.1 g, 3.5 mmol) in CH$_3$CN (50 mL)

was added Cs$_2$CO$_3$ (3.2 g, 9.8 mmol) and diethyltriflate (1.6g, 5.3 mmol). The mixture was

25   stirred at room temperature for 1h. After removed the solvent, the residue was partitioned

between EtOAc and saturated NaCl. The organic phase was dried over Na$_2$SO$_4$, filtered, and

evaporated under reduced pressure. The crude product was chromatographed on silica gel

(1% to 5% MeOH /CH$_2$Cl$_2$) to afford the diethylphosphonate 9 as a white solid: ^{1}H NMR

(CDCl$_3$) δ 8.35 (d, J = 9 Hz, 2H), 7.96 (d, J = 9 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.85 (d, J =

30   8.4 Hz, 2H), 5.63 (d, J = 5.1 Hz, 1H), 5.18-5.01 (m, 2H), 4.27-4.17 (m, 6H), 3.94-3.67 (m,

7H), 3.20-2.73 (m, 7H), 1.92-1.51 (m, 3H), 1.35 (t, J = 7.2 Hz, 6H), 0.88-0.85 (m, 6H); ^{31}P

NMR (CDCl$_3$) δ 19.2; MS (ESI) 756 (M+Na).

Example 9

Amine 10 A solution of diethylphosphonate 9 (1 g) was dissolved in EtOH (100 mL), treated

with 10% Pd/C (300 mg) and was stirred under H_2 atmosphere (balloon) for 3h. The reaction

was purged with N_2, and the catalyst was removed by filtration through celite. After

5   evaporation of the filtrate, the residue was triturated with ether and the solid was collected by

filtration to afford the amine 10 (920 mg, 96%) as a white solid. ^{1}H NMR (CDCl$_3$) ^{1}H NMR

(CDCl$_3$) δ 7.41 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.68 (d,

J = 8.4 Hz, 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.13-5.05 (m, 2H), 4.42 (s, 2H), 4.29-4.20 (m, 6H),

4.00-3.69 (m, 7H), 3.00-2.66 (m, 7H), 1.80-1.69 (m, 3H), 1.38 (m, 6H), 0.94 (d, J = 6.4 Hz,

10   3H), 0.86 (d, J = 6.4 Hz, 6H); ^{31}P NMR (CDCl$_3$) δ 19.4; MS (ESI) 736 (M+Na).

Compound	R₁	R₂
16a	Gly-Et	Gly-Et
16b	Gly-Bu	Gly-Bu
16j	Phe-Bu	Phe-Bu
16k	NHEt	NHEt

Example 10

15   Synthesis of Bisamidates 16a. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-

alanine ethyl ester hydrochloride (84 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and

the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a

solution of Ph$_3$P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in

pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under

20   reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-

propanol/CH$_2$Cl$_2$). The purified product was suspended in ether and was evaporated under

reduced pressure to afford bisamidate 16a (90 mg, 72%) as a white solid: ^{1}H NMR (CDCl$_3$)

δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7

Hz , 2H), 5.68 (d, J = 5.1 Hz,, 1H), 5.05 (m, 1H), 4.25 (d, J = 9.9 Hz, 2H), 4.19 (q, 4H),

25   3.99-3.65 (m overlapping s, 13H,), 3.41 (m, 1H), 3.20-2.81 (m, 7H), 1.85-1.60 (m, 3H), 1.27

(t, J = 7.2 Hz, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ

21.8; MS (ESI) 843 (M+H).

Example 11

Synthesis of Bisamidates 16b. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-alanine n-butyl ester hydrochloride (101 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph$_3$P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH$_2$Cl$_2$). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16b (100 mg, 74%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 2H), 7.01 (d, J = 9 Hz, 2H), 6.87 (d, J = 9 Hz, 2H), 5.67 (d, J = 5.4 Hz, 1H), 5.05 (m, 1H), 4.96 (m, 1H), 4.25 (d, J = 9.9 Hz, 2H), 4.11 (t, J = 6.9 Hz, 4H), 3.99-3.71 (m overlapping s, 13H,), 3.41 (m, 1H), 3.20-2.80 (m, 7H), 1.87-1.60 (m, 7H), 1.42 (m, 4H), 0.96-0.88 (m, 12H); ^{31}P NMR (CDCl$_3$) δ 21.8; MS (ESI) 890 (M+H).

Example 12

Synthesis of Bisamidates 16j. A solution of phosphonic acid 11 (100 mg, 0.15 mmol) L-phenylalanine n-butyl ester hydrochloride (155 mg, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph$_3$P (118 mg, 0.45 mmol) and 2,2'-dipyridyl disulfide (99 mg, 0.45 mmol) in pyridine (1 mL) stirring for 36h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH$_2$Cl$_2$). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16j (106 mg, 66%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.31-7.10 (m, 12H), 7.01 (d, J = 9 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.05 (m, 1H), 4.96 (m, 1H), 4.35-3.98 (m., 7H), 3.90-3.61 (m overlapping s, 10H,), 3.19-2.78 (m, 11H), 1.87-1.25 (m, 11H), 0.96-0.88 (m, 12H); ^{31}P NMR (CDCl$_3$) δ 19.3; MS (ESI) 1080 (M+H).

Example 13

Synthesis of Bisamidates 16k. A solution of phosphonic acid 11 (80 mg, 0.12 mmol), ethylamine (0.3 mL,2M in THF, 0.6 mmol) was dissolved in pyridine (5 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph$_3$P (109 mg, 0.42 mmol) and 2,2'-dipyridyl disulfide (93 mg, 0.42 mmol) in pyridine (1 mL) stirring for 48h at room temperature. The solvent was evaporated under reduced

pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH$_2$Cl$_2$). The purified product was suspended in ether and was evaporated under reduced pressure to afford bisamidate 16k (60 mg, 70%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz , 2H), 5.67 (d, J = 5.1 Hz, 1H), 5.05-4.95 (m, 2H), 4.15 (d, J = 9.6 Hz, 2H), 3.99-3.72 (m overlapping s, 9H,), 3.18-2.81 (m, 11H), 2.55 (br, 1H), 1.85-1.65 (m, 3H), 1.18 (t, J = 7.2 Hz, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 21.6; MS (ESI) 749 (M+Na).

Compound	R$_1$	R$_2$
30a	OPh	Ala-Me
30b	OPh	Ala-Et
30c	OPh	(D)-Ala-iPr
30d	OPh	Ala-Bu
30e	OBn	Ala-Et

Example 14

Monoamidate 30a (R1 = OPh, R2 = Ala-Me)   To a flask was charged with monophenyl phosphonate 29 (75 mg, 0.1 mmol), L-alanine methyl ester hydrochloride (4.0 g, 22 mmol) and 1, 3-dicyclohexylcarbodiimide (84 mg, 0.6 mmol), then pyridine (1 mL) was added under N2. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between ethyl acetate and HCl (0.2 N), the ethyl acetate phase was washed with water and NaHCO$_3$, dried over Na$_2$SO$_4$ filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:5) to give 30a (25 mg, 30%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.01 (m, 2H), 4.30 (m, 2H), 3.97-3.51 (m overlapping s, 12H), 3.20-2.77 (m, 7H), 1.81 (m, 1H), 1.58 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.4 and 19.3; MS (ESI) 856 (M+Na).

Example 15

Monoamidate 30b (R1 = OPh, R2 = Ala-Et) was synthesized in the same manner in 35% yield. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.01 (m, 3H), 4.30 -3.67

(m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.22 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.4 and 19.3; MS (ESI) 870 (M+Na).

Example 16

Monoamidate 30c (R1 = OPh, R2 = (D)-Ala-iPr) was synthesized in the same manner in 52% yield. Isomer A ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.66 (m,, 1H), 5.01 (m, 3H), 4.30 -3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.23 (m, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.4; MS (ESI) 884 (M+Na). Isomer B ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.66 (m,, 1H), 5.01 (m, 3H), 4.30 -3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.23 (m, 6H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 19.3; MS (ESI) 884 (M+Na).

Example 17

Monoamidate 30d (R1 = OPh, R2 = Ala-Bu) was synthesized in the same manner in 25% yield. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.24 (m, 5H) 7.19-7.15 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.90-6.83 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.01 (m, 3H), 4.30 -3.67 (m overlapping s, 16H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 8H), 1.22 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.4 and 19.4; MS (ESI) 898 (M+Na).

Example 18

Monoamidate 30e (R1 = OBn, R2 = Ala-Et) To a flask was charged with monobenzyl phosphonate 2 (76 mg, 0.1 mmol), L-alanine methyl ester hydrochloride (4.0 g, 22 mmol) and 1, 3-dicyclohexylcarbodiimide (84 mg, 0.6 mmol), then pyridine (1 mL) was added under N2. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was partitioned between ethyl acetate and HCl (0.2 N), the ethyl acetate phase was washed with water and NaHCO$_3$, dried over Na$_2$SO$_4$ filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate / hexane 1:5) to give 30a (25 mg, 30%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.38-7.34 (m, 5H), 7.13

(d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.86-6.80 (m, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.15-5.01 (m, 5H), 4.30 -3.67 (m overlapping s, 14H), 3.18-2.77 (m, 7H), 1.81-1.35 (m, 6H), 1.22 (m, 3H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 23.3 and 22.4; MS (ESI) 884 (M+Na).

Compound	R$_1$	R$_2$
31a	OPh	Lac-iPr
31b	OPh	Lac-Et
31c	OPh	Lac-Bu
31d	OPh	(R)-Lac-Me
31e	OPh	(R)-Lac-Et

Example 19

Monolactate 31a (R1 = OPh, R2 = Lac-iPr): To a flask was charged with monophenyl phosphonate 29 (1.5 g, 2 mmol), isopropyl-(s)-lactate (0.88 mL, 6.6 mmol) and 1, 3-dicyclohexylcarbodiimide (1.36 g, 6.6 mmol), then pyridine (15 mL) was added under N$_2$. The resulted mixture was stirred at 60 – 70°C for 2 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered and the filtrate was evaporated. The residue was washed with ethyl acetate and the combined organic phase was washed with NH$_4$Cl, brine and water, dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (ethyl acetate / CH$_2$Cl$_2$ 1:5) to give 31a (1.39g, 81%) as a white solid. Isomer A ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.15 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 5.65 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 4H), 4.56-4.44 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.13-2.78 (m, 7H), 1.81-1.23 (m, 6H), 1.22 (m, 6H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 17.4; MS (ESI) 885 (M+Na). Isomer B ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.64 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 4H), 4.53 -4.41 (m, 2H), 3.96 -3.68 (m overlapping s, 9H), 3.13-2.78 (m, 7H), 1.81-1.23 (m, 6H), 1.22 (m, 6H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 15.3; MS (ESI) 885 (M+Na).

Example 20

Monolactate 31b (R1 = OPh, R2 = Lac-Et) was synthesized in the same manner in 75% yield. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.63 (m, 1H), 5.19-4.95 (m, 3H), 4.44-4.40 (m, 2H), 4.17-4.12 (m,

2H), 3.95 -3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-1.58 (m, 6H), 1.23 (m, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 17.5 and 15.4; MS (ESI) 872 (M+Na).

5   Example 21

Monolactate 31c (R1 = OPh, R2 = Lac-Bu) was synthesized in the same manner in 58% yield. Isomer A ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.63 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 3H), 4.56-4.51 (m, 2H), 4.17-4.10 (m, 2H), 3.95 -3.67 (m overlapping s, 9H), 3.10-

10   2.77 (m, 7H), 1.81-1.23 (m, 10H), 1.23 (m, 6H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 17.3; MS (ESI) 899 (M+Na). Isomer B ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.73-7.19 (m, 5H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.64 (d, J= 5.4 Hz, 1H), 5.15-5.00 (m, 3H), 4.44 -4.39 (m, 2H), 4.17-4.10 (m, 2H), 3.95 -3.67 (m overlapping s, 9H), 3.10-2.77 (m, 7H), 1.81-1.23 (m, 10H), 1.23 (m,

15   6H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 15.3; MS (ESI) 899 (M+Na).

Example 22

Monolactate 31d (R1 = OPh, R2 = (R)-Lac-Me): To a stirred solution of monophenyl

20   phosphonate 29 (100 mg, 0.13 mmol) in 10 mL of THF at room temperature under N$_2$ was added methyl-(S)-lactate (54 mg, 0.52 mmol) and Ph$_3$P (136 mg g,, 0.52 mmol), followed by DEAD (82μL, 0.52 mmol). After 2 h, the solvent was removed under reduced pressure, and the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane 1:1) to give 31d (33 mg, 30%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7

25   Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.63 (m, 1H), 5.19-4.95 (m, 3H), 4.44-4.40 (m, 2H), 3.95 -3.64 (m overlapping s, 12H), 3.15-2.77 (m, 7H), 1.81-1.55 (m, 4H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 17.4 and 15.3; MS (ESI) 857 (M+Na).

30   Example 23

Monolactate 31e (R1 = OPh, R2 = (R)-Lac-Et): To a stirred solution of monophenyl phosphonate 29 (50 mg, 0.065 mmol) in 2.5 mL of THF at room temperature under N$_2$ was

added ethyl-(s)-lactate.(31 mg, 0.52 mmol) and Ph$_3$P (68 mg g, 0.26 mmol), followed by

DEAD (41μL, 0.52 mmol). After 2 h, the solvent was removed under reduced pressure, and

the resulting crude mixture was purified by chromatography on silica gel (ethyl acetate /

hexane 1:1) to give 31e (28 mg, 50%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7

5   Hz, 2H), 7.73-7.14 (m, 7H), 6.99 (d, J = 8.7 Hz, 2H), 6.85(m, 2H), 5.63 (m, 1H), 5.19-4.95

(m, 3H), 4.44-4.40 (m, 2H), 4.17-4.12 (m, 2H), 3.95 -3.67 (m overlapping s, 9H), 3.15-2.77

(m, 7H), 1.81-1.58 (m, 6H), 1.23 (m, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H);

^{31}P NMR (CDCl$_3$) δ 17.5 and 15.4; MS (ESI) 872 (M+Na).

10   Example 24

Monolactate 32 (R1 = OBn, R2 = (S)-Lac-Bn): To a stirred solution of monobenzyl

phosphonate 2 (76 mg, 0.1 mmol) in 0.5 mL of DMF at room temperature under N$_2$ was

added benzyl-(s)-lactate (27 mg, 0.15 mmol) and PyBOP (78 mg, 0.15mmol), followed by

DIEA (70μL, 0.4 mmol). After 3 h, the solvent was removed under reduced pressure, and the

15   resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane

1:1) to give 32 (46 mg, 50%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H),

7.38-7.44 (m, 10H), 7.13 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.81(m, 2H), 5.63 (d, J

= 5.1 Hz, 1H), 5.23-4.92 (m, 7H), 4.44-22 (m, 2H), 3.96 -3.67 (m overlapping s, 9H), 3.15-

2.77 (m, 7H), 1.81-1.58 (m, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR

20   (CDCl$_3$) δ 20.8 and 19.6; MS (ESI) 947 (M+Na).

Example 25

Monolactate 33 (R1 = OBn, R2 = (R)-Lac-Bn): To a stirred solution of monobenzyl

phosphonate 2 (76 mg, 0.1 mmol) in 5 mL of THF at room temperature under N$_2$ was added

25   benzyl-(s)-lactate (72 mg, 0.4 mmol) and Ph$_3$P (105 mg g, 0.4mmol), followed by DEAD

(60μL, 0.4 mmol). After 20 h, the solvent was removed under reduced pressure, and the

resulting crude mixture was purified by chromatography on silica gel (ethyl acetate / hexane

1:1) to give 33 (44 mg, 45%) as a white solid. ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H),

7.38-7.44 (m, 10H), 7.13 (m, 2H), 6.99 (d, J = 8.7 Hz, 2H), 6.81(m, 2H), 5.63 (m, 1H), 5.23-

30   4.92 (m, 7H), 4.44-22 (m, 2H), 3.96 -3.67 (m overlapping s, 9H), 3.15-2.77 (m, 7H), 1.81-

1.58 (m, 6H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.8

and 19.6; MS (ESI) 947 (M+Na).

Example 26

Monophosphonic acid 34: A solution of monobenzyllactate 32 (20 mg) was dissolved in EtOH/ EtOAc (3 mL/1 mL), treated with 10% Pd/C (4 mg) and was stirred under H2

5   atmosphere (balloon) for 1.5 h. The catalyst was removed by filtration through celite. The filtered was evaporated under reduced pressure, the residue was triturated with ether and the solid was collected by filtration to afford the monophosphonic acid 33 (15 mg, 94%) as a white solid. ^{1}H NMR (CD$_3$OD) δ 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.69 (d, J = 5.7 Hz, 1H), 5.03-4.95 (m, 2H), 4.20 (m,

10   2H), 3.90 -3.65 (m overlapping s, 9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 2.00 (m, 1H), 1.61-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 18.0; MS (ESI) 767 (M+Na).

Example 27

15   Monophosphonic acid 35: A solution of monobenzyllactate 33 (20 mg) was dissolved in EtOH (3 mL), treated with 10% Pd/C (4 mg) and was stirred under H2 atmosphere (balloon) for 1h. The catalyst was removed by filtration through celite. The filtered was evaporated under reduced pressure, the residue was triturated with ether and the solid was collected by filtration to afford the monophosphonic acid 35 (15 mg, 94%) as a white solid. ^{1}H NMR

20   (CD$_3$OD) δ 7.76 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.69 (d, J = 5.7 Hz, 1H), 5.03-4.95 (m, 2H), 4.20 (m, 2H), 3.90 -3.65 (m overlapping s, 9H), 3.41 (m, 2H), 3.18-2.78 (m, 5H), 2.44 (m, 1H), 2.00 (m, 1H), 1.61-1.38 (m, 5H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 18.0; MS (ESI) 767 (M+Na).

25

Example 28

Synthesis of Bislactate 36: A solution of phosphonic acid 11 (100 mg, 0.15 mmol) isopropyl-(S)-lactate (79 mg, 0.66 mmol) was dissolved in pyridine (1 mL) and the solvent was distilled under reduced pressure at 40-60°C. The residue was treated with a solution of Ph$_3$P

30   (137 mg, 0.53 mmol) and 2,2'-dipyridyl disulfide (116 mg, 0.53 mmol) in pyridine (1 mL) stirring for 20h at room temperature. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (1% to 5% 2-propanol/CH$_2$Cl$_2$). The purified product was suspended in ether and was evaporated under reduced pressure to afford

bislactate 36 (42 mg, 32%) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.66 (d, J = 5.1 Hz, 1H), 5.05 (m, 3H), 4.25 (d, J = 9.9 Hz, 2H), 4.19 (q, 4H), 3.99-3.65 (m overlapping s, 9H,), 3.41 (m, 1H), 3.20-2.81 (m, 7H), 1.85-1.60 (m, 3H),1.58 (m, 6H), 1.26 (m, 12H), 0.93 (d, J = 6.3 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 21.1; MS (ESI) 923 (M+Na).

Example 29

Triflate derivative 1: A THF-CH$_2$Cl$_2$ solution (30mL-10 mL) of 8 (4 g, 6.9 mmol), cesium carbonate (2.7 g, 8 mmol), and N-phenyltrifluoromethane sulfonimide (2.8 g, 8 mmol) was reacted overnight. The reaction mixture was worked up, and concentrated to dryness to give crude triflate derivative 1.

Aldehyde 2: Crude triflate 1 (4.5 g, 6.9 mmole) was dissolved in DMF (20 mL), and the solution was degassed (high vacuum for 2 min, Ar purge, repeat 3 times). Pd(OAc)2 (0.12 g, 0.27 mmol), and bis(diphenylphosphino)propane (dppp, 0.22 g, 0.27 mmol) were added and the solution was heated to 70°C. Carbon monoxide was rapidly bubbled through the solution, then under 1 atmosphere of carbon monoxide. To this solution were slowly added TEA (5.4 mL, 38 mmol), and triethylsilane (3 mL, 18 mmol). The resulting solution was stirred overnight at room temperature. The reaction mixture was worked up, and purified on silica gel column chromatograph to afford aldehyde 2 (2.1 g, 51%). (Hostetler, et al. J. Org. Chem., 1999. 64, 178-185).

Lactate prodrug 4: Compound 4 is prepared as described above procedure for 3a-e by the reductive amination between 2 and 3 with NaBH$_3$CN in 1,2-dichloroethane in the presence of HOAc.
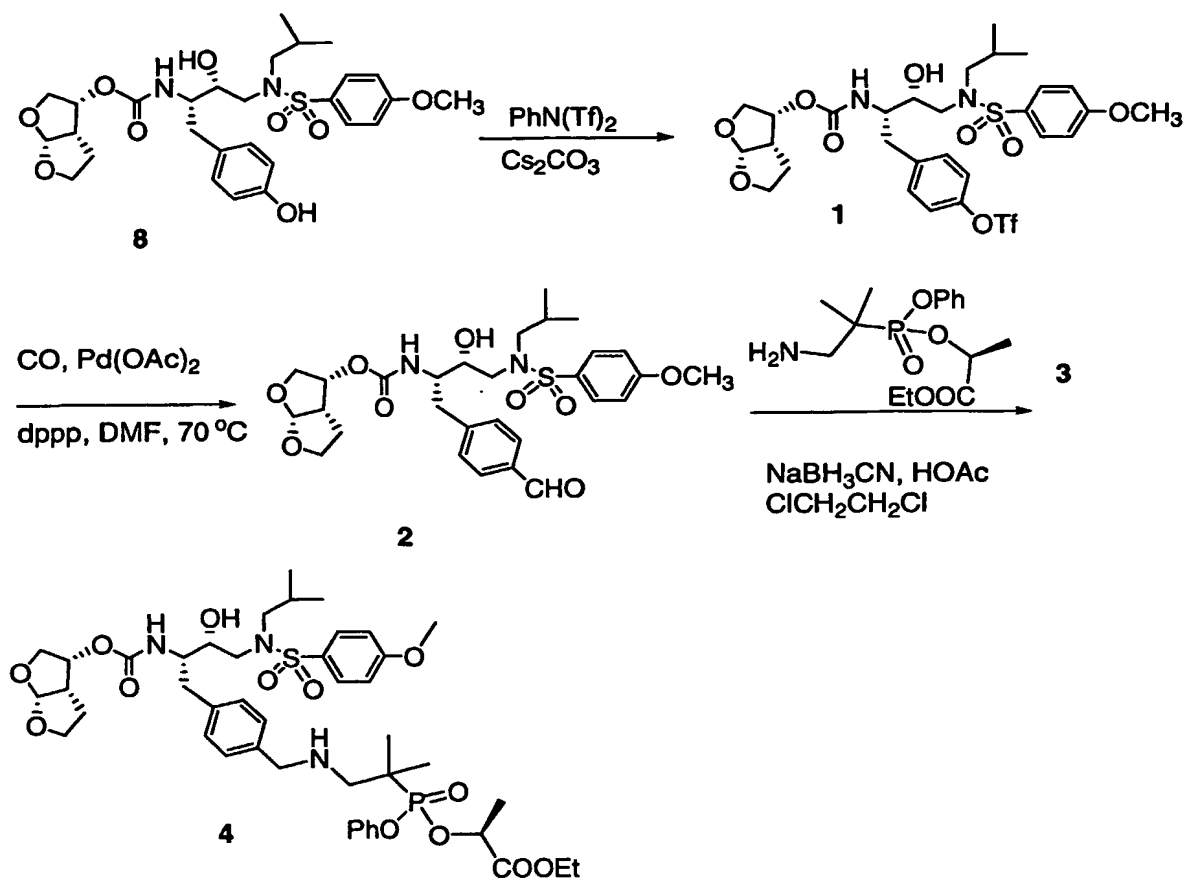
Example 30

Preparation of compound 3 Diethyl (cyano(dimethyl)methyl) phosphonate 5: A THF

5   solution (30 mL) of NaH (3.4 g of 60% oil dispersion, 85 mmole) was cooled to -10°C,

followed by the addition of diethyl (cyanomethyl)phosphonate (5g, 28.2 mmol) and

iodomethane (17 g, 112 mmol). The resulting solution was stirred at -10°C for 2 hr, then 0°C

for 1 hr, was worked up, and purified to give dimethyl derivative 5 (5 g, 86%).

Dietyl (2-amino-1,1-diemthyl-ethyl)phosphonate 6: Compound 5 was reduced to amine

10   derivative 6 by the described procedure (J. Med. Chem. 1999, 42, 5010-5019).

A ethanol (150 mL) and 1N HCl aqueous solution (22 mL) of 5 (2.2 g, 10.7 mmol) was

hydrogenated at 1 atmosphere in the presence of PtO_2 (1.25 g) at room temperature

overnight. The catalyst was filtered through a celite pad. The filtrate was concentrated to

dryness, to give crude 6 (2.5g, as HCl salt).

15

2-Amino-1,1-dimethyl-ethyl phosphonic acid 7: A CH_3CN (30 mL) of crude 6 (2.5 g) was

cooled to 0°C, and treated with TMSBr (8 g, 52 mmol) for 5 hr. The reaction mixture was

stirred with methanol for 1.5 hr at room temperature, concentrated, recharged with methanol, concentrated to dryness to give crude **7** which was used for next reaction without further purification.

5　　Lactate phenyl (2-amino-1,1-diemthyl-ethyl)phosphonate **3**: Compound **3** is synthesized according to the procedures described in a previous scheme for the preparation of a lactate phenyl 2-aminoethyl phosponate. Compound **7** is protected with CBZ, followed by the reaction with thionyl chloride at 70°C.. The CBZ protected dichlorodate is reacted phenol in the presence of DIPEA. Removal of one phenol, follow by coupling with ethyl L-lactate

10　　leads N-CBZ-2-amino-1,1-dimethyl-ethyl phosphonated derivative. Hydrogenation of N-CBZ derivative at 1 atmosphere in the presence of 10% Pd/C and 1 equivalent of TFA affords compound **3** as TFA salt.
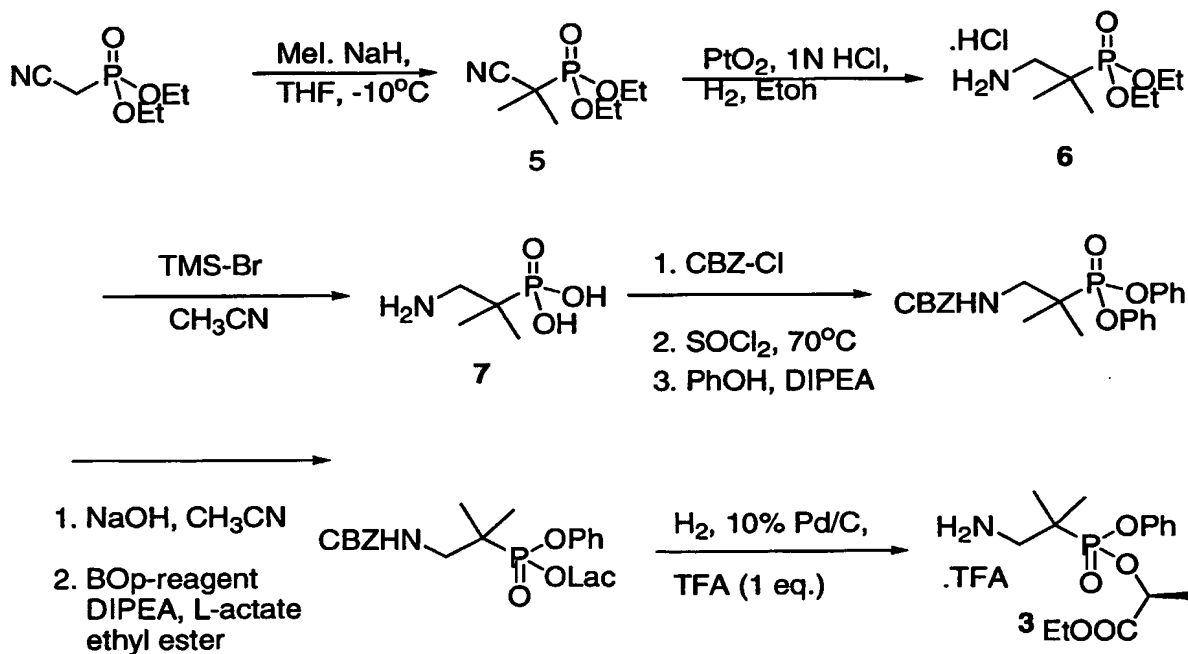
Example Section M

Scheme 1

Scheme 2

5 $\xrightarrow[\text{Cs}_2\text{CO}_3,\ \text{CH}_3\text{CN}]{\text{TfO}\frown\text{P(O)(OBn)}_2}$

6

$\xrightarrow[\text{(2)} \bigcirc\!\!-\!\!\text{SO}_2\text{Cl}\quad \text{TEA, CH}_2\text{Cl}_2]{\text{(1) TFA, CH}_2\text{Cl}_2}$

7
GS 191477

$\xrightarrow[\text{MeOH, r.t.}]{\text{Pd / C, H}_2}$

8
GS 191478

6 $\xrightarrow[\text{(2) NC}\!\!-\!\!\bigcirc\!\!-\!\!\text{SO}_2\text{Cl}\quad \text{TEA, CH}_2\text{Cl}_2]{\text{(1) TFA, CH}_2\text{Cl}_2}$

9
GS 191717

Scheme 3

10
GS 191479

11
GS 191480

12
GS 191482

13
GS 191483

Scheme 4

6 $\xrightarrow[\text{TEA, CH}_2\text{Cl}_2]{\text{(1) TFA, CH}_2\text{Cl}_2 \quad \text{(2) } F_3CO\text{-}C_6H_4\text{-}SO_2Cl}$

14
GS 191508

$\xrightarrow[\text{MeOH, r.t.}]{\text{Pd / C, H}_2}$

15
GS 192041

6 $\xrightarrow[\text{TEA, CH}_2\text{Cl}_2]{\text{(1) TFA, CH}_2\text{Cl}_2 \quad \text{(2) HCl.N-SO}_2\text{Cl}}$

16
GS 273805

$\xrightarrow[\text{MeOH / AcOH}]{\text{Pd / C, H}_2}$

17
GS 273845

Scheme 5

6 → (1) TFA, CH₂Cl₂ / (2) ClO₂S—⟨ ⟩—CHO, TEA, CH₂Cl₂ → **18** GS 278114

Pd / C, H₂, EtOAc, r.t. → **19**

(1) BSA, CH₃CN, reflux / (2) Morpholine, NaBH₃CN, HOAc, EtOAc → **20 (GS 278118) R = OH** / **21 (GS 278117) R = N⌒O**

Example 1

5   Cbz Amide 1: To a suspension of epoxide (34 g, 92.03 mmol) in 2-propanol (300 mL) was
      added isobutylamine (91.5 mL, 920 mmol) and the solution was refluxed for 1 h. The
      solution was evaporated under reduced pressure and the crude solid was dried under vacuum
      to give the amine (38.7 g, 95%) which was dissolved in CH₂Cl₂ (300 mL) and cooled to 0°C.
      Triethylamine (18.3 mL, 131 mmol) was added followed by the addition of benzyl

10   chloroformate (13.7 mL, 96.14 mmol) and the solution was stirred for 30 min at 0°C, warmed
      to room temperature overnight, and evaporated under reduced pressure. The residue was
      partitioned between EtOAc and 0.5 M H₃PO₄. The organic phase was washed with saturated
      NaHCO₃, brine, dried with Na₂SO₄, filtered, and evaporated under reduced pressure. The

crude product was purified by column chromatography on silica gel (1/2-EtOAc/hexane) to give the Cbz amide (45.37 g, 90%) as a white solid.

Example 2

5   Amine 2: A solution of Cbz amide 1 (45.37 g, 78.67 mmol) in CH_2Cl_2 (160 mL) at $0^\circ C$ was treated with trifluoroacetic acid (80 mL). The solution was stirred for 30 min at $0^\circ C$ and then warmed to room temperature for an additional 30 min. Volatiles were evaporated under reduced pressure and the residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2 x), water (2 x), saturated NaCl, dried with

10   Na_2SO_4, filtered, and evaporated under reduced pressure to give the amine (35.62 g, 95%) as a white solid.

Example 3

Carbamate 3: To a solution of amine 2 (20.99 g, 44.03 mmol) in CH_3CN (250 mL) at $0^\circ C$

15   was treated with (3R, 3aR, 6aS)-hexahydrofuro[2, 3-b]furan-2-yl 4-nitrophenyl carbonate (13.00 g, 44.03 mmol, prepared according to Ghosh et al. J. Med. Chem. 1996, 39, 3278.), N,N-diisopropylethylamine (15.50 mL, 88.06 mmol) and 4-dimethylaminopyridine (1.08 g, 8.81 mmol). The reaction mixture was stirred at $0^\circ C$ for 30 min and then warmed to room temperature overnight. The reaction solvent was evaporated under reduced pressure and the

20   residue was partitioned between EtOAc and 0.5 N NaOH. The organic phase was washed with 0.5 N NaOH (2 x), 5% citric acid (2 x), saturated $NaHCO_3$, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the carbamate (23.00 g, 83%) as a white solid.

25

Example 4

Amine 4: To a solution of 3 (23.00 g, 36.35 mmol) in EtOH (200 mL) and EtOAc (50 mL) was added 20% $Pd(OH)_2/C$ (2.30 g). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 3 h. The reaction mixture was filtered through a plug of

30   celite. The filtrate was concentrated and dried under vacuum to give the amine (14.00 g, 94%) as a white solid.

Example 5

Phenol 5: To a solution of amine 4 (14.00 g, 34.27 mmol) in H_2O (80 mL) and 1,4-dioxane (80 mL) at 0°C was added Na_2CO_3 (5.09 g, 47.98 mmol) and di-*tert*-butyl dicarbonate (8.98 g, 41.13 mmol). The reaction mixture was stirred at 0°C for 2 h and then warmed to room temperature for 30 min. The residue was partitioned between EtOAc and H_2O. The organic layer was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% $MeOH/CH_2Cl_2$) to give the phenol (15.69 g, 90%) as a white solid.

Example 6

Dibenzylphosphonate 6: To a solution of phenol 5 (15.68 g, 30.83 mmol) in CH_3CN (200 mL) was added Cs_2CO_3 (15.07 g, 46.24 mmol) and triflate (17.00 g, 40.08 mmol). The reaction mixture was stirred at room temperature for 1 h, the salt was filtered off, and the solvent was evaporated under reduced pressure. The residue was partitioned between EtOAc and saturated NaCl. The organic phase was dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the dibenzylphosphonate (15.37 g, 73%) as a white solid.

Example 7

Sulfonamide 7: A solution of dibenzylphosphonate 6 (0.21 g, 0.26 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.15 mL, 1.04 mmol) was added followed by the treatment of benzenesulfonyl chloride (47 mg, 0.26 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide 7 (0.12 g, 55%, GS 191477) as a white solid: ^{1}HNMR ($CDCl_3$) δ 7.79 (dd, 2H), 7.61-7.56 (m, 3H), 7.38-7.36 (m, 10H), 7.13 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.18 (m, 4H), 5.05 (m, 1H), 4.93 (d, J = 8.7 Hz, 1H), 4.20 (d, J = 10.2 Hz, 2H), 4.0-3.67 (m, 7H), 3.15-2.8 (m, 7H), 1.84 (m, 1H),

1.65-1.59 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.36.

Example 8

5   Phosphonic Acid 8: To a solution of 7 (70 mg, 0.09 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (49 mg, 90% GS 191478) as a white solid: ^{1}HNMR (CD$_3$OD) δ 7.83 (dd, 2H), 7.65-7.56 (m, 3H), 7.18 (d, J

10   = 8.4 Hz, 2H), 6.91 (d, J = 7.8 Hz, 2H), 5.59 (d, J = 5.4 Hz, 1H), 4.96 (m, 1H), 4.15 (d, J = 9.9 Hz, 2H), 3.95-3.68 (m, 6H), 3.44 (dd, 2H), 3.16 (m, 2H), 2.99-2.84 (m, 4H), 2.48 (m, 1H), 2.02 (m, 1H), 1.6 (m, 1H), 1.37 (m, 1H), 0.93 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 17.45.

15   Example 9

Sulfonamide 9: A solution of dibenzylphosphonate 6 (0.24 g, 0.31 mmol) in CH$_2$Cl$_2$ (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was

20   co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH$_2$Cl$_2$ (3 mL) and cooled to 0°C. Triethylamine (0.17 mL, 1.20 mmol) was added followed by the treatment of 4-cyanobenzenesulfonyl chloride (61.4 mg, 0.30 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH$_2$Cl$_2$ and saturated NaHCO$_3$. The organic phase

25   was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the sulfonamide 9 (0.20 g, 77%, GS 191717) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.90 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 7.8 Hz, 2H), 7.36 (m, 10H), 7.11 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.2-4.9 (m, 5H), 4.8 (d, 1H),

30   4.2 (d, J = 9.9 Hz, 2H), 3.99 (m 1H), 3.94 (m, 3H), 3.7 (m, 2H), 3.48 (broad, s, 1H), 3.18-2.78 (m, 7H), 1.87 (m, 1H), 1.66-1.47 (m, 2H), 0.91 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.3..

Example 10

Sulfonamide 10: A solution of dibenzylphosphonate 6 (0.23 g, 0.29 mmol) in CH₂Cl₂ (0.5

mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30

5   min at 0°C and then warmed to room temperature for an additional 30 min. The reaction

mixture was diluted with toluene and concentrated under reduced pressure. The residue was

co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the

ammonium triflate salt which was dissolved in CH₂Cl₂ (3 mL) and cooled to 0°C.

Triethylamine (0.16 mL, 1.17 mmol) was added followed by the treatment of 4-

10   trifluoromethyl benzenesulfonyl chloride (72 mg, 0.29 mmol). The solution was stirred for 1

h at 0°C and the product was partitioned between CH₂Cl₂ and saturated NaHCO₃. The

organic phase was washed with saturated NaCl, dried with Na₂SO₄, filtered, and evaporated

under reduced pressure. The crude product was purified by column chromatography on silica

gel (3% 2-propanol/CH₂Cl₂) to give the sulfonamide (0.13 g, 50%, GS 191479) as a white

15   solid: ¹H NMR (CDCl₃) δ 7.92 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.1 Hz, 2H), 7.36 (m, 10H),

7.12 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.20-4.89 (m, 6H),

4.20 (d, J = 9.9 Hz, 2H), 3.95 (m, 1H), 3.86 (m, 3H), 3.71 (m, 2H), 3.19-2.78 (m, 7H), 1.86

(m, 1H), 1.65 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ³¹P NMR (CDCl₃) δ

20.3.

20

Example 11

Phosphonic Acid 11: To a solution of 10 (70 mg, 0.079 mmol) in MeOH (4 mL) was added

10% Pd/C (20 mg). The suspension was stirred under H₂ atmosphere (balloon) at room

temperature overnight. The reaction mixture was filtered through a plug of celite. The

25   filtrate was concentrated and dried under vacuum to give the phosphonic acid (50 mg, 90%,

GS 191480) as a white solid: ¹H NMR (CD₃OD) δ 8.03 (dd, 2H), 7.90 (dd, 2H), 7.17 (d, J =

8.1 Hz, 2H), 6.91 (d, J = 7.8 Hz, 2H), 5.59 (d, J = 5.7 Hz, 1H), 4.94 (m, 1H), 4.15 (d, J = 10.2

Hz, 2H), 3.94-3.72 (m, 6H), 3.48 (m, 1H), 3.2-3.1 (m, 3H), 3.0-2.9 (m, 2H), 2.47 (m, 1H),

2.06 (m, 1H), 1.56 (m, 1H), 1.37 (m, 1H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H);

30   ³¹P NMR (CD₃OD) δ 17.5.

Example 12

Sulfonamide 12: A solution of dibenzylphosphonate 6 (0.23 g, 0.29 mmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction

5   mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.16 mL, 1.17 mmol) was added followed by the treatment of 4-fluorobenzenesulfonyl chloride (57 mg, 0.29 mmol). The solution was stirred for 1 h at 0°C

10   and the product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.13 g, 55%, GS 191482) as a white solid: ^{1}H NMR ($CDCl_3$) δ 7.81 (m, 2H), 7.38 (m, 10H), 7.24 (m, 2H), 7.12 (d, J = 8.1 Hz, 2H), 6.82 (d,

15   J = 8.4 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.17 (m, 4H), 5.0 (m, 1H), 4.90 (d, 1H), 4.20 (d, J = 9.9 Hz, 2H), 3.97 (m, 1H), 3.86 (m, 3H), 3.73 (m, 2H), 3.6 (broad, s, 1H), 3.13 (m, 1H), 3.03-2.79 (m, 6H), 1.86 (m, 1H), 1.66-1.58 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.3.

20   Example 13

Phosphonic Acid 13: To a solution of 12 (70 mg, 0.083 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (49 mg, 90%,

25   GS 191483) as a white solid: ^{1}H NMR (CD_3OD) δ 7.89 (m, 2H), 7.32 (m, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.9 (d, J = 8.1 Hz, 2H), 5.59 (d, J = 5.1 Hz, 1H), 4.94 (m, 1H), 4.16 (d, J = 9.9 Hz, 2H), 3.94 (m, 1H), 3.85-3.7 (m, 5H), 3.43 (dd, 1H), 3.15-2.87 (m, 5H), 2.48 (m, 1H), 2.03 (m, 1H), 1.59-1.36 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD_3OD) δ 17.5.

30

Example 14

Sulfonamide 14: A solution of dibenzylphosphonate 6 (0.21 g, 0.26 mmol) in CH$_2$Cl$_2$ (0.5 mL) at 0°C was treated with trifluoroacetic acid (0.25 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was

5   co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH$_2$Cl$_2$ (3 mL) and cooled to 0°C. Triethylamine (0.15 mL, 1.04 mmol) was added followed by the treatment of 4-trifluoromethoxybenzenesulfonyl chloride (69 mg, 0.26 mmol). The solution was stirred for 1 h at 0°C and the product was partitioned between CH$_2$Cl$_2$ and saturated NaHCO$_3$. The

10   organic phase was washed with saturated NaCl, dried with Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the sulfonamide (0.17 g, 70%, GS 191508) as a white solid: ^{1}H NMR (CDCl$_3$) δ 7.84 (d, J = 9 Hz, 2H), 7.36 (m, 12H), 7.12 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.16 (m, 4H), 5.03 (m, 1H), 4.89 (d, 1H),

15   4.2 (d, J = 9.9 Hz, 2H), 3.97 (m, 1H), 3.85 (m, 3H), 3.7 (m, 2H), 3.59 (broad, s, 1H), 3.18 (m, 1H), 3.1-3.0 (m, 3H), 2.96-2.78 (m, 3H), 1.86 (m, 1H), 1.66-1.5 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{1}P NMR (CDCl$_3$) δ 20.3.

Example 15

20   Phosphonic Acid 15: To a solution of 14 (70 mg, 0.083 mmol) in MeOH (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H$_2$ atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (50 mg, 90%, GS 192041) as a white solid: ^{1}H NMR (CD$_3$OD) δ 7.95 (dd, 2H), 7.49 (dd, 2H), 7.17 (dd,

25   2H), 6.92 (dd, 2H), 5.58 (d, J = 5.4 Hz, 1H), 4.89 (m, 1H), 4.17 (d, J = 9 Hz, 2H), 3.9 (m, 1H), 3.82-3.7 (m, 5H), 3.44 (m, 1H), 3.19-2.9 (m, 5H), 2.48 (m, 1H), 2.0 (m, 1H), 1.6 (m, 1H), 1.35 (m, 1H), 0.93 (d, J = 6.0 Hz, 3H), 0.88 (d, J = 6.0 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 17.4.

30   Example 16

Sulfonamide 16: A solution of dibenzylphosphonate 6 (0.59 g, 0.76 mmol) in CH$_2$Cl$_2$ (2.0 mL) at 0°C was treated with trifluoroacetic acid (1.0 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction

mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the ammonium triflate salt which was dissolved in CH_2Cl_2 (3 mL) and cooled to 0°C. Triethylamine (0.53 mL, 3.80 mmol) was added followed by the treatment of hydrogen

5   chloride salt of 3-pyridinylsulfonyl chloride (0.17 g, 0.80 mmol, prepared according to Karaman, R. et al. J. Am. Chem. Soc. 1992, 114, 4889). The solution was stirred for 30 min at 0°C and warmed to room temperature for 30 min. The product was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was

10   purified by column chromatography on silica gel (4% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.50 g, 80%, GS 273805) as a white solid: ^1H NMR (CDCl$_3$) δ 9.0 (d, J = 1.5 Hz, 1H), 8.8 (dd, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.48 (m, 1H), 7.36 (m, 10H), 7.12 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 5.65 (d, J = 5.1 Hz, 1H), 5.18 (m, 4H), 5.06 (m, 1H), 4.93 (d, 1H), 4.21 (d, J = 8.4 Hz, 2H), 3.97 (m, 1H), 3.86 (m, 3H), 3.74 (m, 2H), 3.2 (m, 1H), 3.1-

15   2.83 (m, 5H), 2.76 (m, 1H), 1.88 (m, 1H), 1.62 (m, 2H), 0.92 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CDCl$_3$) δ 20.3.

Example 17

Phosphonic Acid 17: To a solution of 16 (40 mg, 0.049 mmol) in MeOH (3 mL) and AcOH

20   (1 mL) was added 10% Pd/C (10 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature overnight. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (28 mg, 90%, GS 273845) as a white solid: ^1H NMR (CD$_3$OD) δ 8.98 (s, 1H), 8.77 (broad, s, 1H), 8.25 (dd, 1H), 7.6 (m, 1H), 7.15 (m, 2H), 6.90 (m, 2H), 5.6 (d, J = 5.4 Hz, 1H), 4.98 (m,

25   1H), 4.15 (d, 2H), 3.97-3.7 (m, 6H), 3.45-2.89 (m, 6H), 2.50 (m, 1H), 2.0 (m, 1H), 1.6-1.35 (m, 2H), 0.9 (m, 6H).

Example 18

Sulfonamide 18: A solution of dibenzylphosphonate 6 (0.15 g, 0.19 mmol) in CH_2Cl_2 (0.60

30   mL) at 0°C was treated with trifluoroacetic acid (0.30 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was diluted with toluene and concentrated under reduced pressure. The residue was co-evaporated with toluene (2 x), chloroform (2 x), and dried under vacuum to give the

ammonium triflate salt which was dissolved in CH_2Cl_2 (2 mL) and cooled to 0°C. Triethylamine (0.11 mL, 0.76 mmol) was added followed by the treatment of 4-formylbenzenesulfonyl chloride (43 mg, 0.21 mmol). The solution was stirred for 30 min at 0°C and warmed to room temperature for 30 min. The product was partitioned between

5   CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with saturated NaCl, dried with Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH_2Cl_2) to give the sulfonamide (0.13 g, 80%, GS 278114) as a white solid: ^1H NMR ($CDCl_3$) δ 10.1 (s, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.94 (d, J = 8.1 Hz, 2H), 7.35 (m, 10H), 7.13 (m, J = 8.1 Hz, 2H),

10   6.82 (d, J = 8.1 Hz, 2H), 5.65 (d, J = 5.4 Hz, 1H), 5.17 (m, 4H), 5.06 (m, 1H), 4.93 (m, 1H), 4.2 (d, J = 9.9 Hz, 2H), 3.94 (m, 1H), 3.85 (m, 3H), 3.7 (m, 2H), 3.18-2.87 (m, 5H), 2.78 (m, 1H), 1.86 (m, 1H), 1.67-1.58 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR ($CDCl_3$) δ 20.3.
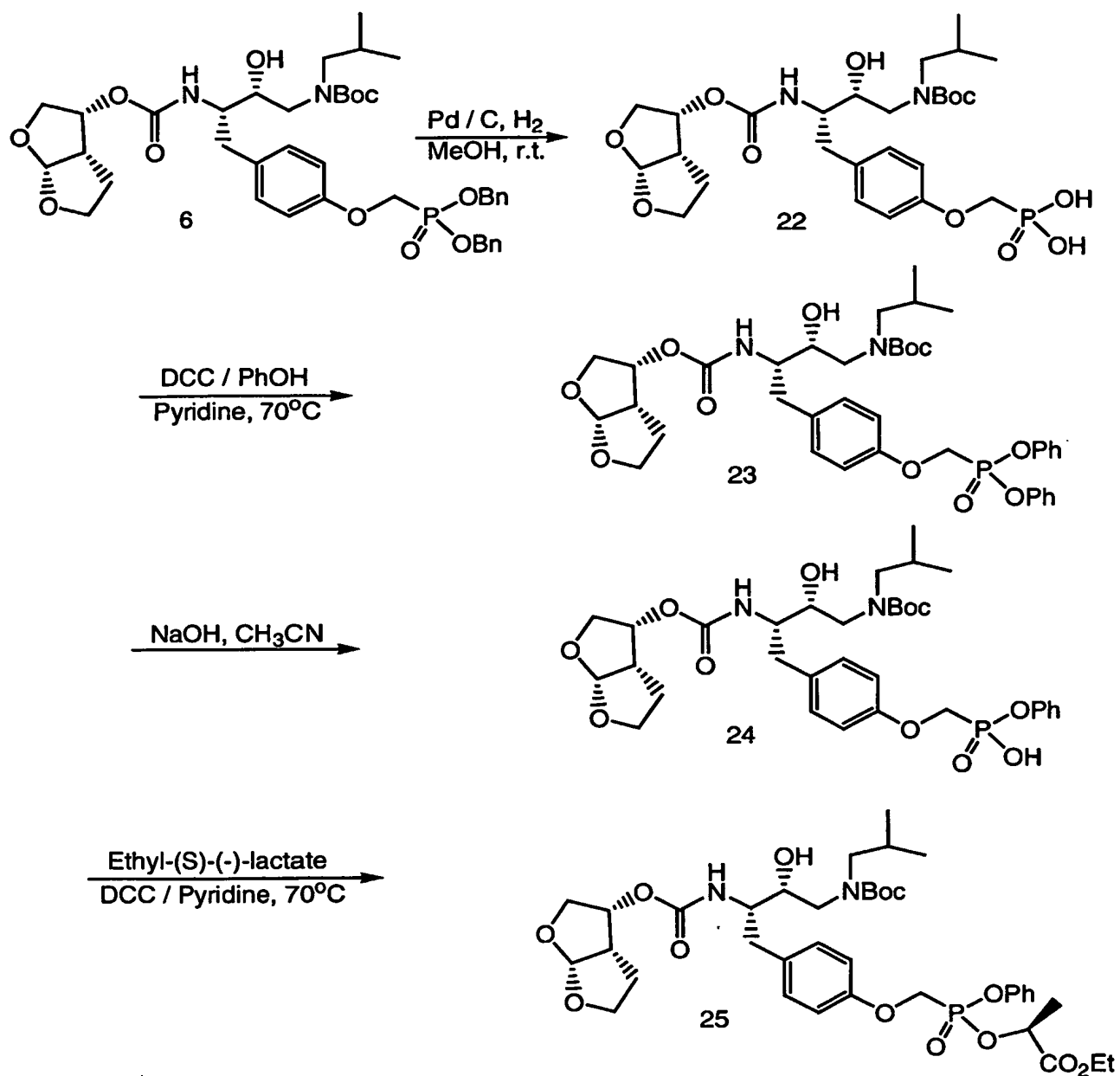
15   <u>Example 19</u>

Phosphonic Acid 19: To a solution of 18 (0.12 g, 0.15 mmol) in EtOAc (4 mL) was added 10% Pd/C (20 mg). The suspension was stirred under H_2 atmosphere (balloon) at room temperature for 6 h. The reaction mixture was filtered through a plug of celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid (93 mg, 95%) as a

20   white solid.

<u>Example 20</u>

Phosphonic Acids 20 and 21: Compound 19 (93 mg, 0.14 mmol) was dissolved in CH_3CN (2 mL). N,O-Bis(trimethylsilyl)acetamide (BSA, 0.28 g, 1.4 mmol) was added. The reaction

25   mixture was heated to reflux for 1 h, cooled to room temperature and concentrated. The residue was co-evaporated with toluene and chloroform and dried under vacuum to give a semi-solid which was dissolved in EtOAc (2 mL). Morpholine (60 μL, 0.9 mmol), AcOH (32 μL, 0.56 mmol), and $NaBH_3CN$ (17 mg, 0.28 mmol) were added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with H_2O, stirred for

30   2 h, filtered, and concentrated. The crude product was purified by HPLC to give the phosphonic acid 20 (10 mg, GS 278118) as a white solid: ^1H NMR (CD_3OD) δ 7.80 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 7.5 Hz, 2H), 7.17 (d, J = 7.8 Hz, 2H), 6.91 (d, J = 7.5 Hz, 2H), 5.59

(d, J = 5.1 Hz, 1H), 5.06 (m, 1H), 4.7 (s, 2H), 4.15 (d, J = 10.2 Hz, 2H), 3.92 (m, 1H), 3.82-3.7 (m, 5H), 3.43 (dd, 1H), 3.11-2.89 (m, 6H), 2.50 (m, 1H), 2.0 (m, 1H), 1.6-1.35 (m, 2H), 0.93 (d, J = 6.3 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 17.3.   Phosphonic acid 21 (15 mg, GS 278117) as a white solid: ^{1}H NMR (CD$_3$OD) δ 7.8-7.7 (m, 4H), 7.20 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 5.62 (d, J = 5.1 Hz, 1H), 5.00 (m, 1H), 4.42 (s, 2H), 4.20 (dd, 2H), 3.98-3.68 (m, 9H), 3.3-2.92 (m, 11H), 2.6 (m, 1H), 2.0 (m, 1H), 1.6 (m, 2H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{31}P NMR (CD$_3$OD) δ 16.2.

Scheme 6

Pd / C, H$_2$
MeOH, r.t.

6 → 22

DCC / PhOH
Pyridine, 70°C

23

NaOH, CH$_3$CN

24

Ethyl-(S)-(-)-lactate
DCC / Pyridine, 70°C

25

Scheme 7

25   (1) TFA / CH$_2$Cl$_2$ (2) ⬡—SO$_2$Cl   TEA / CH$_2$Cl$_2$

26
GS 192779

25   (1) TFA / CH$_2$Cl$_2$ (2) F—⬡—SO$_2$Cl   TEA / CH$_2$Cl$_2$

27
GS 192776

25   (1) TFA / CH$_2$Cl$_2$ (2) HCl.N⬡—SO$_2$Cl   TEA / CH$_2$Cl$_2$

28
GS 273806

*m*CPBA, CH$_2$Cl$_2$

29
GS 273851

Scheme 8

28 $\xrightarrow{\text{MeOTf}}{\text{CHCl}_3}$

30
GS 273813

16 $\xrightarrow{\text{MeOTf, CHCl}_3}$

31
GS 273812

16 $\xrightarrow{m\text{CPBA}}{\text{CH}_2\text{Cl}_2}$

32
GS 277774

$\xrightarrow{\text{Pd / C, H}_2}{\text{MeOH, r.t.}}$

33
GS 277775

Scheme 9

25   (1) TFA / CH$_2$Cl$_2$

(2) ClO$_2$S—⟨C$_6$H$_4$⟩—CHO

TEA / CH$_2$Cl$_2$

34
GS 278052

Morpholine, NaBH$_3$CN
HOAc, EtOAc, r.t.

35
GS 278115

25   (1) TFA / CH$_2$Cl$_2$

(2) TEA / CH$_2$Cl$_2$

BnO—⟨C$_6$H$_4$⟩—SO$_2$Cl
36

37

Pd / C, H$_2$
EtOH, r.t.

38
GS 273838

Scheme 10

25 $\xrightarrow{\begin{array}{c}(1)\ \text{TFA} / \text{CH}_2\text{Cl}_2 \\ \hline (2)\ \text{CbzN}\underset{\mathbf{39}}{\bigcirc}\text{N}-\bigcirc-\text{SO}_2\text{Cl} \\ \text{TEA} / \text{CH}_2\text{Cl}_2\end{array}}$

40

$\xrightarrow{\begin{array}{c}\text{Pd} / \text{C, H}_2, \text{TFA} \\ \hline \text{MeOH} / \text{EtOAc}\end{array}}$

41

$\xrightarrow{\begin{array}{c}\text{HCHO} / \text{HOAc} \\ \hline \text{NaBH}_3\text{CN, EtOAc}\end{array}}$

42
GS 277937

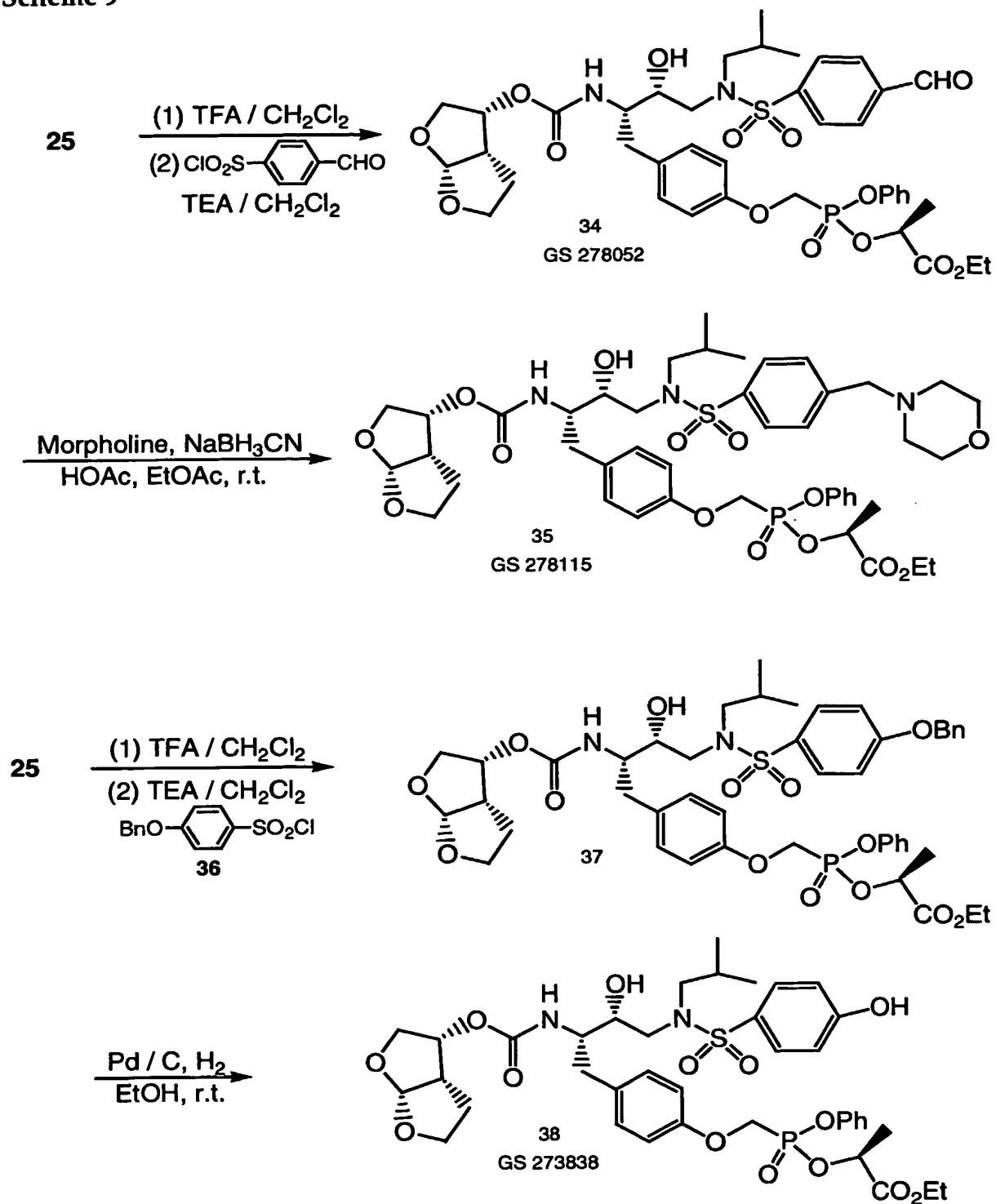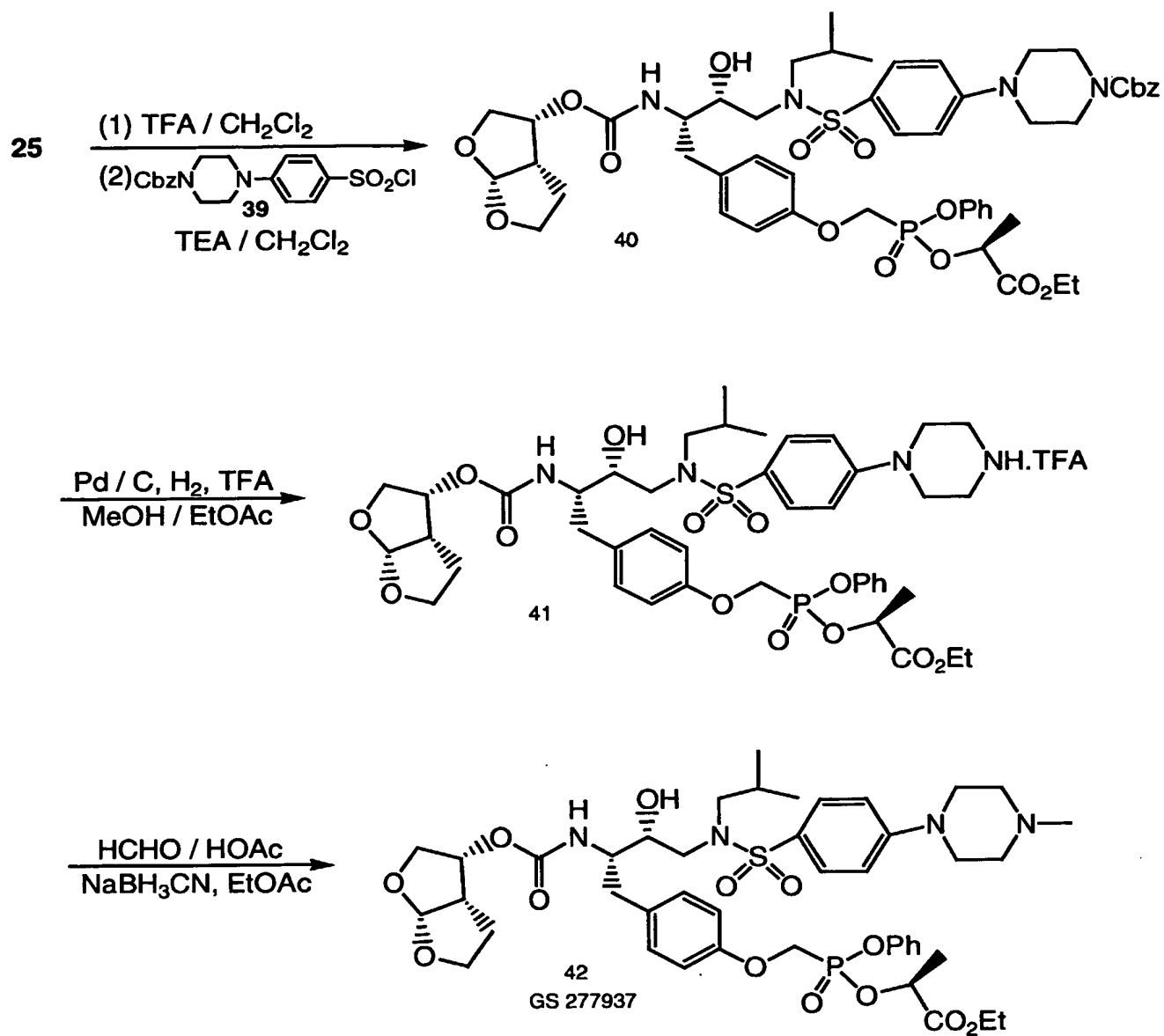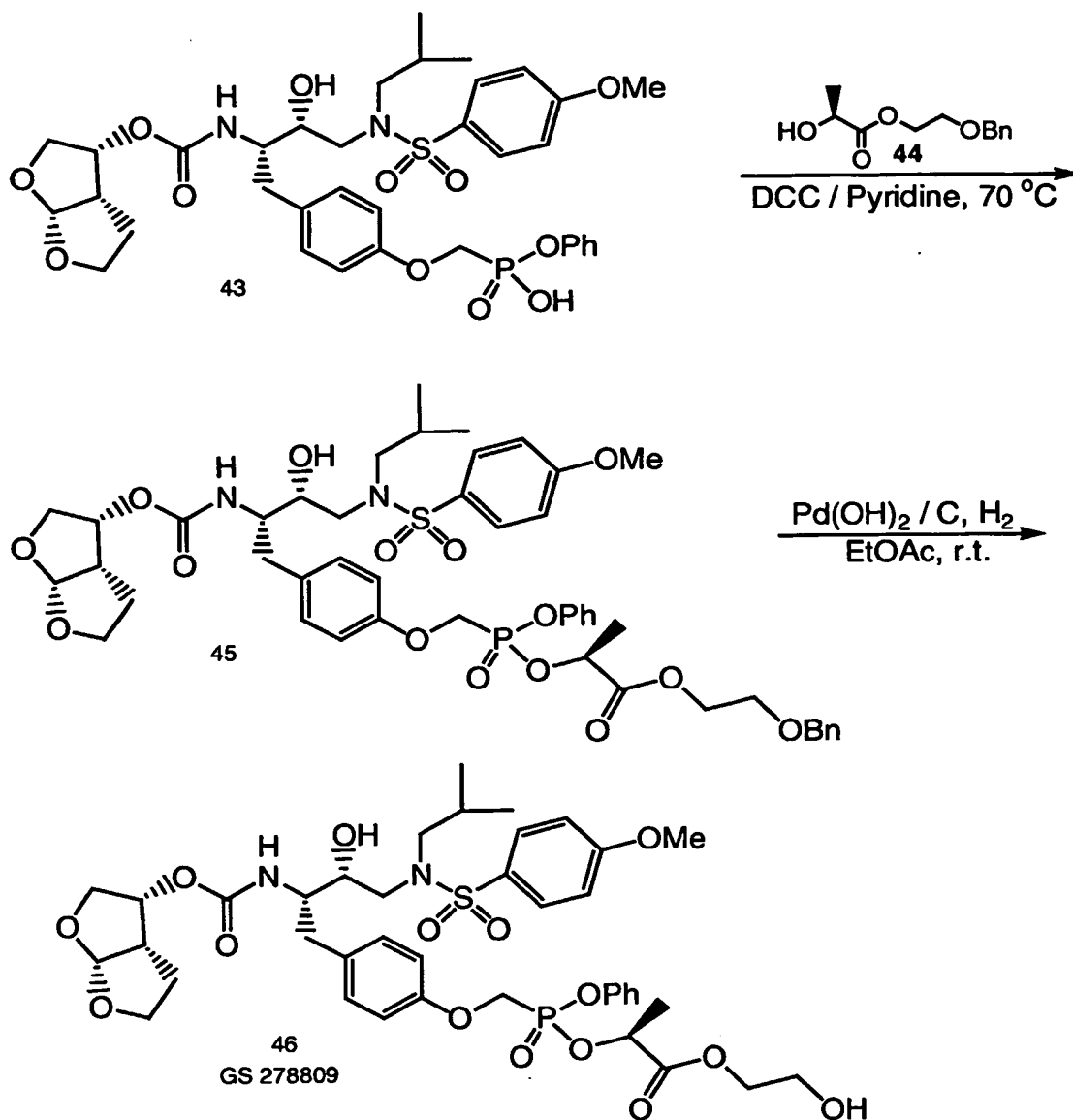**Scheme 11**

5   <u>Example 21</u>

Phosphonic Acid 22: To a solution of dibenzylphosphonate 6 (5.00 g, 6.39 mmol) in EtOH
(100 mL) was added 10% Pd/C (1.4 g). The suspension was stirred under H_2 atmosphere
(balloon) at room temperature overnight. The reaction mixture was filtered through a plug of
celite. The filtrate was concentrated and dried under vacuum to give the phosphonic acid

10   (3.66 g, 95%) as a white solid.

<u>Example 22</u>

Diphenylphosphonate 23: A solution of 22 (3.65 g, 6.06 mmol) and phenol (5.70 g, 60.6 mmol) in pyridine (30 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (5.00 g, 24.24 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. EtOAc was added and the side product 1,3-dicyclohexyl urea was filtered off.

5 The filtrate was concentrated and dissolved in CH$_3$CN (20 mL) at 0°C. The mixture was treated with DOWEX 50W x 8-400 ion-exchange resin and stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the diphenylphosphonate (2.74 g, 60%) as a white solid.

10

Example 23

Monophosphonic Acid 24: To a solution of 23 (2.74 g, 3.63 mmol) in CH$_3$CN (40 mL) at 0°C was added 1 N NaOH (9.07 mL, 9.07 mmol). The reaction mixture was stirred at 0°C for 1 h. DOWEX 50W x 8-400 ion-exchange resin was added and the reaction mixture was

15 stirred for 30 min at 0°C. The resin was filtered off and the filtrate was concentrated and co-evaporated with toluene. The crude product was triturated with EtOAc/hexane (1/2) to give the monophosphonic acid (2.34 g, 95%) as a white solid.

Example 24

20 Monophospholactate 25: A solution of 24 (2.00 g, 2.95 mmol) and ethyl-(S)-(-)-lactate (1.34 mL, 11.80 mmol) in pyridine (20 mL) was heated to 70°C and 1,3-dicyclohexylcarbodiimide (2.43 g, 11.80 mmol) was added. The reaction mixture was stirred at 70°C for 2 h and cooled to room temperature. The solvent was removed under reduced pressure. The residue was suspended in EtOAc and 1,3-dicyclohexyl urea was filtered off. The product was partitioned

25 between EtOAc and 0.2 N HCl. The EtOAc layer was washed with 0.2 N HCl, H$_2$O, saturated NaCl, dried with Na$_2$SO$_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (3% 2-propanol/CH$_2$Cl$_2$) to give the monophospholactate (1.38 g, 60%) as a white solid.

30 Example 25

Monophospholactate 26: A solution of 25 (0.37 g, 0.48 mmol) in CH$_2$Cl$_2$ (0.80 mL) at 0°C was treated with trifluoroacetic acid (0.40 mL). The solution was stirred for 30 min at 0°C and then warmed to room temperature for an additional 30 min. The reaction mixture was

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